IRAK DEGRADERS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Appl. No. 62/949,298, filed on December 17, 2019, and U.S. Provisional Appl. No. 63/040,906, filed on June 18, 2020, the content of each of which is hereby incorporated by reference.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to compounds and methods useful for the modulation of one or more interleukin-1 receptor-associated kinases ("IRAK") via ubiquitination and/or degradation by compounds according to the present invention. The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0003] Ubiquitin-Proteasome Pathway (UPP) is a critical pathway that regulates key regulator proteins and degrades misfolded or abnormal proteins. UPP is central to multiple cellular processes, and if defective or imbalanced, it leads to pathogenesis of a variety of diseases. The covalent attachment of ubiquitin to specific protein substrates is achieved through the action of E3 ubiquitin ligases.

[0004] There are over 600 E3 ubiquitin ligases which facilitate the ubiquitination of different proteins in vivo, which can be divided into four families: HECT-domain E3s, U-box E3s, monomeric RING E3s and multi-subunit E3s. See generally Li et al. (PLOS One, 2008, 3, 1487) titled "Genome-wide and functional annotation of human E3 ubiquitin ligases identifies MULAN, a mitochondrial E3 that regulates the organelle's dynamics and signaling."; Berndsen et al. (Nat. Struct. Mol. Biol., 2014, 21, 301-307) titled "New insights into ubiquitin E3 ligase mechanism"; Deshaies et al. (Ann. Rev. Biochem., 2009, 78, 399-434) titled "RING domain E3 ubiquitin ligases."; Spratt et al. (Biochem. 2014, 458, 421-437) titled "RBR E3 ubiquitin ligases: new structures, new insights, new questions."; and Wang et al. (Nat. Rev. Cancer., 2014, 14, 233-347) titled "Roles of F-box proteins in cancer."

[0005] UPP plays a key role in the degradation of short-lived and regulatory proteins important in a variety of basic cellular processes, including regulation of the cell cycle, modulation of cell surface receptors and ion channels, and antigen presentation. The pathway has been implicated in several forms of malignancy, in the pathogenesis of several genetic diseases (including cystic fibrosis, Angelman's syndrome, and Liddle syndrome), in immune surveillance/viral pathogenesis, and in the pathology of muscle wasting. Many diseases are associated with an abnormal UPP and negatively affect cell cycle and

division, the cellular response to stress and to extracellular modulators, morphogenesis of neuronal networks, modulation of cell surface receptors, ion channels, the secretory pathway, DNA repair and biogenesis of organelles.

[0006] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result from gain of function, i.e. abnormal or accelerated degradation of the protein target.

[0007] The UPP is used to induce selective protein degradation, including use of fusion proteins to artificially ubiquitinate target proteins and synthetic small-molecule probes to induce proteasome-dependent degradation. Bifunctional compounds composed of a target protein-binding ligand and an E3 ubiquitin ligase ligand, induced proteasome-mediated degradation of selected proteins via their recruitment to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds are capable of inducing the inactivation of a protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, 17(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(l):40-46).

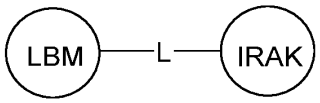
[0008] An ongoing need exists in the art for effective treatments for disease, especially hyperplasias and cancers, such as multiple myeloma. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated proteins such as interleukin-1 receptor-associated kinases ("IRAK") hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are IRAK degraders useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0009] The present application relates novel bifunctional compounds, which function to recruit IRAK kinases to E3 Ubiquitin Ligase for degradation, and methods of preparation and uses thereof. In particular, the present disclosure provides bifunctional compounds, which find utility as modulators of targeted ubiquitination of IRAK kinases, which are then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of IRAK kinases. In addition, the description provides methods of using an effective amount of the compounds as described

herein for the treatment or amelioration of a disease condition, such as cancer, e.g., multiple myeloma.

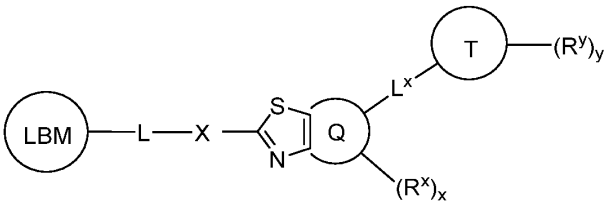
[0010] The present application further relates to targeted degradation of IRAK kinases through the use of bifunctional molecules, including bifunctional molecules that link a degradation inducing moiety to a ligand that binds IRAK kinases having the following general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0011] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective for the modulation of targeted ubiquitination. Such compounds have the formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0012] The present invention further relates to bifunctional compounds that not only degrade IRAK, but also degrade IMiD substrates, such as Ikaros, Aiolos, or Ikaros and Aiolos.

[0013] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of signaling pathways implicating IRAK kinases. Such diseases, disorders, or conditions include those described herein.

[0014] Compounds provided by this invention are also useful for the study of IRAK enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new IRAK inhibitors or IRAK degraders or other regulators of kinases, signaling pathways, and cytokine levels in vitro or in vivo.

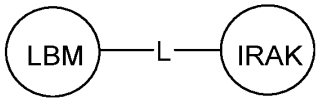
DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

[0015] Compounds of the present invention, and compositions thereof, are useful as degraders and/or inhibitors of one or more IRAK protein kinases. In some embodiments, a provided compound degrades and/or inhibits IRAK-1/2/3/4. In some embodiments, a provided compound degrades IRAK4 and IMiD

substrates, such as Ikaros, Aiolos, or Ikaros and Aiolos.

[0016] In certain embodiments, the present invention provides a compound of formula **I**:



I

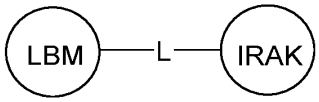
or a pharmaceutically acceptable salt thereof, wherein:

IRAK is an IRAK binding moiety capable of binding to one or more of IRAK1, IRAK2, IRAK3, and IRAK4;

L is a bivalent moiety that connects IRAK to LBM; and

LBM is a cereblon E3 ubiquitin ligase binding moiety.

[0017] In certain embodiments, the present invention provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

IRAK is an IRAK binding moiety capable of binding to IRAK4;

L is a bivalent moiety that connects IRAK to LBM; and

LBM is a IMiD-based cereblon E3 ubiquitin ligase binding moiety.

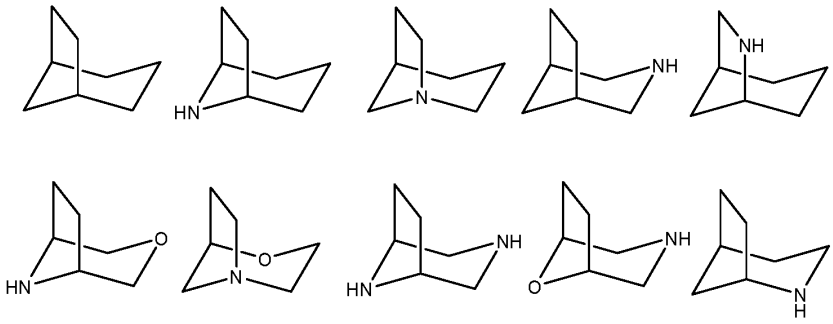
2. Compounds and Definitions:

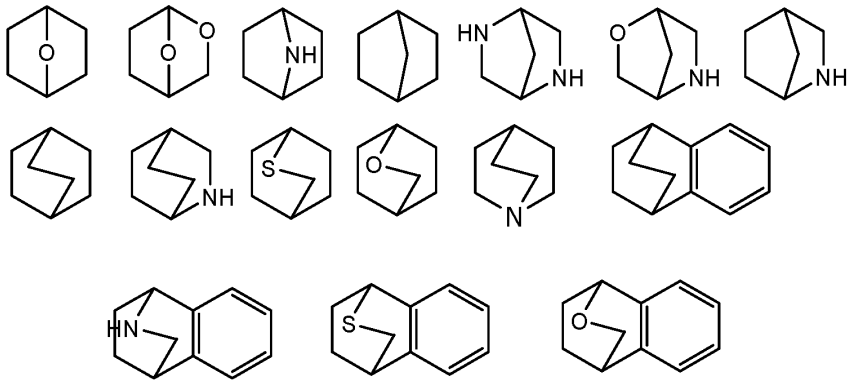
[0018] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0019] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment

to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0020] As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bridged bicyclics include:





[0021] The term "lower alkyl" refers to a C_{1-4} straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0022] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

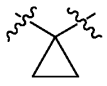
[0023] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0024] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0025] As used herein, the term "bivalent C_{1-8} (or C_{1-6}) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0026] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0027] The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0028] As used herein, the term "cyclopropylenyl" refers to a bivalent cyclopropyl group of the following structure:  .

[0029] The term "halogen" means F, Cl, Br, or I.

[0030] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present invention, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non–aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0031] The terms "heteroaryl" and "heteroar–," used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3–b]–1,4–oxazin–3(4H)–one. A heteroaryl group may be mono– or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0032] As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring" are used interchangeably and refer to a stable 5– to 7–membered monocyclic or 7–10–membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur

or nitrogen, the nitrogen may be N (as in 3,4–dihydro–2*H*–pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in *N*–substituted pyrrolidinyl).

[0033] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle," "heterocyclyl," "heterocyclyl ring," "heterocyclic group," "heterocyclic moiety," and "heterocyclic radical," are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be monocyclic, bicyclic, bridged bicyclic, or spirocyclic. A heterocyclyl group may contain one or more =O ("oxo") or =S ("thio-oxo") group. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0034] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0035] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted" means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0036] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $–(CH_2)_{0–4}R°$; $–(CH_2)_{0–4}OR°$; $-O(CH_2)_{0-4}R°$, $–O–(CH_2)_{0–4}C(O)OR°$; $–(CH_2)_{0–4}CH(OR°)_2$; $–(CH_2)_{0–4}SR°$; $–(CH_2)_{0–4}Ph$, which may be substituted with R°; $–(CH_2)_{0–4}O(CH_2)_{0–1}Ph$ which may be substituted with R°; –CH=CHPh, which may be substituted with R°; $–(CH_2)_{0–4}O(CH_2)_{0–1}$-pyridyl which may be substituted with R°; $–NO_2$; –CN; $–N_3$; $-(CH_2)_{0–4}N(R°)_2$; $–(CH_2)_{0–4}N(R°)C(O)R°$; $–N(R°)C(S)R°$; $–(CH_2)_{0–4}N(R°)C(O)NR°_2$; $-N(R°)C(S)NR°_2$; $–(CH_2)_{0–4}N(R°)C(O)OR°$; –

$N(R°)N(R°)C(O)R°$; $-N(R°)N(R°)C(O)NR°_2$; $-N(R°)N(R°)C(O)OR°$; $-(CH_2)_{0-4}C(O)R°$; $-C(S)R°$; $-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}C(O)SR°$; $-(CH_2)_{0-4}C(O)OSiR°_3$; $-(CH_2)_{0-4}OC(O)R°$; $-OC(O)(CH_2)_{0-4}SR-$; $-(CH_2)_{0-4}SC(O)R°$; $-(CH_2)_{0-4}C(O)NR°_2$; $-C(S)NR°_2$; $-C(S)SR°$; $-SC(S)SR°$, $-(CH_2)_{0-4}OC(O)NR°_2$; $-C(O)N(OR°)R°$; $-C(O)C(O)R°$; $-C(O)CH_2C(O)R°$; $-C(NOR°)R°$; $-(CH_2)_{0-4}SSR°$; $-(CH_2)_{0-4}S(O)_2R°$; $-(CH_2)_{0-4}S(O)_2OR°$; $-(CH_2)_{0-4}OS(O)_2R°$; $-S(O)_2NR°_2$; $-(CH_2)_{0-4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $-N(R°)S(O)_2R°$; $-N(OR°)R°$; $-C(NH)NR°_2$; $-P(O)_2R°$; $-P(O)R°_2$; $-OP(O)R°_2$; $-OP(O)(OR°)_2$; $SiR°_3$; $-(C_{1-4}$ straight or branched alkylene$)O-N(R°)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R°)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2-$(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0037] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0038] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0039] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, -(halo$R^\bullet$), -OH, $-OR^\bullet$, -O(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0040] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0041] Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^\bullet$, -(halo$R^\bullet$), –OH, $-OR^\bullet$, -O(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0042] As used herein, the term "provided compound" refers to any genus, subgenus, and/or species set forth herein.

[0043] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate,

hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0044] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0045] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention

[0046] As used herein, the term "inhibitor" is defined as a compound that binds to and/or inhibits an IRAK kinase with measurable affinity. In certain embodiments, an inhibitor has an IC_{50} and/or binding constant of less than about 50 μM, less than about 1 μM, less than about 500 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM.

[0047] As used herein, the term "degrader" is defined as a heterobifunctional or monovalent compound that binds to and/or inhibits both an IRAK kinase and an E3 ligase with measurable affinity resulting in the ubiqitination and subsequent degradation of the IRAK kinase. In certain embodiments, a degrader has an DC_{50} of less than about 50 μM, less than about 1 μM, less than about 500 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM. As used herein, the term "monovalent" refers to a degrader compound without an appended E3 ligase binding moiety.

[0048] A compound of the present invention may be tethered to a detectable moiety. It will be appreciated that such compounds are useful as imaging agents. One of ordinary skill in the art will

recognize that a detectable moiety may be attached to a provided compound *via* a suitable substituent. As used herein, the term "suitable substituent" refers to a moiety that is capable of covalent attachment to a detectable moiety. Such moieties are well known to one of ordinary skill in the art and include groups containing, e.g., a carboxylate moiety, an amino moiety, a thiol moiety, or a hydroxyl moiety, to name but a few. It will be appreciated that such moieties may be directly attached to a provided compound or *via* a tethering group, such as a bivalent saturated or unsaturated hydrocarbon chain. In some embodiments, such moieties may be attached via click chemistry. In some embodiments, such moieties may be attached via a 1,3-cycloaddition of an azide with an alkyne, optionally in the presence of a copper catalyst. Methods of using click chemistry are known in the art and include those described by Rostovtsev *et al.*, Angew. Chem. Int. Ed. 2002, 41, 2596-99 and Sun *et al.*, Bioconjugate Chem., 2006, 17, 52-57.

[0049] As used herein, the term "detectable moiety" is used interchangeably with the term "label" and relates to any moiety capable of being detected, e.g., primary labels and secondary labels. Primary labels, such as radioisotopes (e.g., tritium, ^{32}P, ^{33}P, ^{35}S, or ^{14}C), mass-tags, and fluorescent labels are signal generating reporter groups which can be detected without further modifications. Detectable moieties also include luminescent and phosphorescent groups.

[0050] The term "secondary label" as used herein refers to moieties such as biotin and various protein antigens that require the presence of a second intermediate for production of a detectable signal. For biotin, the secondary intermediate may include streptavidin-enzyme conjugates. For antigen labels, secondary intermediates may include antibody-enzyme conjugates. Some fluorescent groups act as secondary labels because they transfer energy to another group in the process of nonradiative fluorescent resonance energy transfer (FRET), and the second group produces the detected signal.

[0051] The terms "fluorescent label", "fluorescent dye", and "fluorophore" as used herein refer to moieties that absorb light energy at a defined excitation wavelength and emit light energy at a different wavelength. Examples of fluorescent labels include, but are not limited to: Alexa Fluor dyes (Alexa Fluor 350, Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660 and Alexa Fluor 680), AMCA, AMCA-S, BODIPY dyes (BODIPY FL, BODIPY R6G, BODIPY TMR, BODIPY TR, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY 630/650, BODIPY 650/665), Carboxyrhodamine 6G, carboxy-X-rhodamine (ROX), Cascade Blue, Cascade Yellow, Coumarin 343, Cyanine dyes (Cy3, Cy5, Cy3.5, Cy5.5), Dansyl, Dapoxyl, Dialkylaminocoumarin, 4',5'-Dichloro-2',7'-dimethoxy-fluorescein, DM-NERF, Eosin, Erythrosin, Fluorescein, FAM, Hydroxycoumarin, IRDyes (IRD40, IRD 700, IRD 800), JOE, Lissamine rhodamine B, Marina Blue, Methoxycoumarin, Naphthofluorescein, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, PyMPO, Pyrene, Rhodamine B, Rhodamine 6G, Rhodamine Green, Rhodamine Red, Rhodol Green, 2',4',5',7'-Tetra-bromosulfone-fluorescein, Tetramethyl-rhodamine

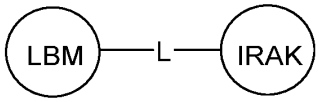
(TMR), Carboxytetramethylrhodamine (TAMRA), Texas Red, Texas Red-X.

[0052] The term "mass-tag" as used herein refers to any moiety that is capable of being uniquely detected by virtue of its mass using mass spectrometry (MS) detection techniques. Examples of mass-tags include electrophore release tags such as N-[3-[4'-[(p-Methoxytetrafluorobenzyl)oxy]phenyl]-3-methylglyceronyl]isonipecotic Acid, 4'-[2,3,5,6-Tetrafluoro-4-(pentafluorophenoxyl)]methyl acetophenone, and their derivatives. The synthesis and utility of these mass-tags is described in United States Patents 4,650,750, 4,709,016, 5,360,8191, 5,516,931, 5,602,273, 5,604,104, 5,610,020, and 5,650,270. Other examples of mass-tags include, but are not limited to, nucleotides, dideoxynucleotides, oligonucleotides of varying length and base composition, oligopeptides, oligosaccharides, and other synthetic polymers of varying length and monomer composition. A large variety of organic molecules, both neutral and charged (biomolecules or synthetic compounds) of an appropriate mass range (100-2000 Daltons) may also be used as mass-tags.

[0053] The terms "measurable affinity" and "measurably inhibit," as used herein, means a measurable change in an IRAK protein kinase activity between a sample comprising a compound of the present invention, or composition thereof, and an IRAK protein kinase, and an equivalent sample comprising an IRAK protein kinase, in the absence of said compound, or composition thereof.

3. Description of Exemplary Embodiments:

[0054] As described above, in certain embodiments, the present invention provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

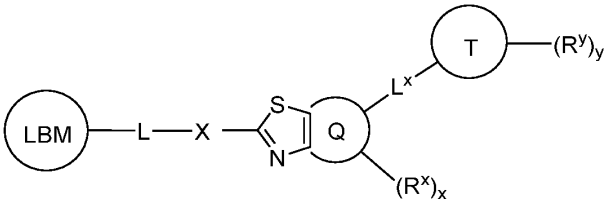
IRAK is an IRAK4 binding moiety;

L is a bivalent moiety that connects IRAK to LBM; and

LBM is a cereblon E3 ubiquitin ligase binding moiety.

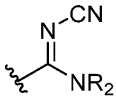
IRAK Binding Moiety (IRAK)

[0055] In certain embodiments, the present invention provides a compound of formula **I**, where IRAK is an IRAK4 binding moiety thereby forming a compound of formula **I-a**:



I-a

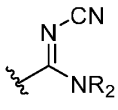
or a pharmaceutically acceptable salt thereof, wherein DIM and L are as defined and described herein, and wherein:

each R^x is independently hydrogen, deuterium, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-N^+(O^-)R_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-P(O)R_2$, $-SiR_3$, $-Si(OR)R_2$, or  ; or

two R^x groups are optionally taken together to form an optionally substituted 5-7 membered partially unsaturated or aryl fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, deuterium, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-SiR_3$, $-SF_5$, or  ;

each R^z is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms

independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring Q is selected from benzo or a fused 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring T is selected from phenyl, a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring T is further optionally substituted with 1-2 oxo groups;

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-Cy^x-$, -O-, -S-, -C(O)-, -C(S)-, $-CR_2-$, -CRF-, $-CF_2-$, -NR-, -N=CR-, -CR=CR-, or $-S(O)_2-$, wherein R of $-CR_2-$, -CRF-, -NR-, -N=CR-, or -CR=CR- can combine with R^x or R^y to form a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

$-Cy^x-$ is an optionally substituted ring selected from a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein $-Cy^x-$ is optionally substituted with 1-2 oxo groups;

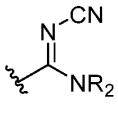
X is a covalent bond or an optionally substituted bivalent ring selected from phenylenyl, a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

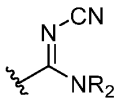
each x is 0, 1, 2, 3 or 4; and

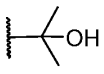
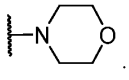
each y is 0, 1, 2, 3 or 4;

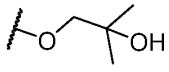
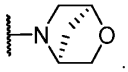
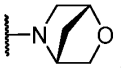
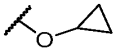
wherein the compound of formula **I-a** is not compound **I-1** or **I-2** in **Table 1A**.

[0056] As defined generally above, each R^x is independently hydrogen, deuterium, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-N^+(O^-)R_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, -

$OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-P(O)R_2$, $-SiR_3$, $-Si(OR)R_2$, or  ; or two R^x groups are optionally taken together to form an optionally substituted 5-7 membered partially unsaturated or aryl fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0057] In some embodiments, each R^x is independently hydrogen. In some embodiments, R^x is deuterium. In some embodiments, each R^x is independently R^z. In some embodiments, each R^x is independently halogen. In some embodiments, each R^x is independently –CN. In some embodiments, each R^x is independently $-NO_2$. In some embodiments, each R^x is independently –OR. In some embodiments, each R^x is independently –SR. In some embodiments, each R^x is independently $-NR_2$. In some embodiments, each R^x is independently $-S(O)_2R$. In some embodiments, each R^x is independently $-S(O)_2NR_2$. In some embodiments, each R^x is independently -S(O)R. In some embodiments, each R^x is independently $-CFR_2$. In some embodiments, each R^x is independently $-CF_2R$. In some embodiments, each R^x is independently $-CF_3$. In some embodiments, each R^x is independently $-CR_2(OR)$. In some embodiments, each R^x is independently $-CR_2(NR_2)$. In some embodiments, each R^x is independently -C(O)R. In some embodiments, each R^x is independently -C(O)OR. In some embodiments, each R^x is independently $-C(O)NR_2$. In some embodiments, each R^x is independently $-N^+(O^-)R_2$. In some embodiments, each R^x is independently $-OP(O)R_2$. In some embodiments, each R^x is independently $-OP(O)(OR)_2$. In some embodiments, each R^x is independently $-OP(O)(OR)NR_2$. In some embodiments, each R^x is independently $-OP(O)(NR_2)_2$. In some embodiments each R^x is independently $-P(O)R_2$. In some embodiments, each R^x is independently $-SiR_3$. In some embodiments, each R^x is independently $-Si(OR)R_2$. In some embodiments, each R^x is independently $-SF_5$. In some embodiments, each R^x is independently  . In some embodiments, two R^x groups are optionally taken together to form an optionally substituted 5-6 membered partially unsaturated or aryl fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, two R^x groups are optionally taken together to form an optionally substituted 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic spiro fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

[0058] In some embodiments, R^x is  . In some embodiments, R^x is $-CF_2H$. In some embodiments, R^x is -OMe. In some embodiments, R^x is -Me. In some embodiments, R^x is $-OCF_2H$. In some embodiments, R^x is $-OCF_3$. In some embodiments, R^x is  . In some embodiments, R^x is

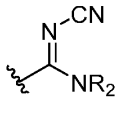
 . In some embodiments, R^x is  . In some embodiments, R^x is  . In some embodiments, R^x is  .

[0059] In some embodiments, each R^x is selected from those depicted in **Table 1**, below.

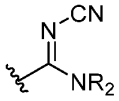
[0060] As generally defined above, each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from nitrogen, oxygen, and sulfur.

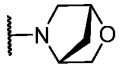
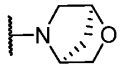
[0061] In some embodiments, each R is independently hydrogen. In some embodiments, each R is an optionally substituted group selected from C_{1-6} aliphatic. In some embodiments, each R is an optionally substituted phenyl. In some embodiments, each R is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each R is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two R groups on the same nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

[0062] In some embodiments, each R is selected from those depicted in **Table 1**, below.

[0063] As defined generally above, each R^y is independently hydrogen, deuterium, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-N^+(O^-)R_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-P(O)R_2$, $-SiR_3$, $-Si(OR)R_2$, $-SF_5$, or  ; or two R^y groups are optionally taken together to form an optionally substituted 5-6 membered partially unsaturated or aryl fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0064] In some embodiments, each R^y is independently hydrogen. In some embodiments, R^y is deuterium. In some embodiments, each R^y is independently R^z. In some embodiments, each R^y is independently halogen. In some embodiments, each R^y is independently –CN. In some embodiments, each

R^y is independently $-NO_2$. In some embodiments, each R^y is independently –OR. In some embodiments, each R^y is independently –SR. In some embodiments, each R^y is independently $-NR_2$. In some embodiments, each R^y is independently $-S(O)_2R$. In some embodiments, each R^y is independently $-S(O)_2NR_2$. In some embodiments, each R^y is independently -S(O)R. In some embodiments, each R^y is independently $-CFR_2$. In some embodiments, each R^y is independently $-CF_2R$. In some embodiments, each R^y is independently $-CF_3$. In some embodiments, each R^y is independently $-CR_2(OR)$. In some embodiments, each R^y is independently $-CR_2(NR_2)$. In some embodiments, each R^y is independently -C(O)R. In some embodiments, each R^y is independently -C(O)OR. In some embodiments, each R^y is independently $-C(O)NR_2$. In some embodiments, each R^y is independently $-N^+(O^-)R_2$. In some embodiments, each R^y is independently $-OP(O)R_2$. In some embodiments, each R^y is independently $-OP(O)(OR)_2$. In some embodiments, each R^y is independently $-OP(O)(OR)NR_2$. In some embodiments, each R^y is independently $-OP(O)(NR_2)_2$. In some embodiments each R^y is independently $-P(O)R_2$. In some embodiments, each R^y is independently $-SiR_3$. In some embodiments, each R^y is independently $-Si(OR)R_2$. In some embodiments, each R^y is independently $-SF_5$. In some embodiments, each R^y is independently  . In some embodiments, two R^y groups are optionally taken together to form an optionally substituted 5-7 membered partially unsaturated or aryl fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0065] In some embodiments, R^y is $-CF_2Me$. In some embodiments, R^y is $-CFMe_2$. In some embodiments, R^y is -Me. In some embodiments, R^y is $-OCF_3$. In some embodiments, R^y is fluoro. In some embodiments, R^y is  . In some embodiments, R^y is  .

[0066] In some embodiments, each R^y is selected from those depicted in **Table 1**, below.

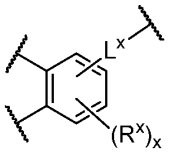
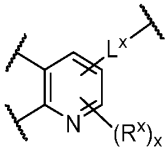
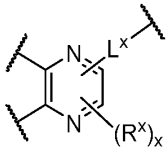
[0067] As generally defined above, each R^z is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0068] In some embodiments, each R^z is independently an optionally substituted group selected from C_{1-6} aliphatic. In some embodiments, each R^z is independently an optionally substituted phenyl. In some embodiments, each R^z is independently an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each R^z is independently an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0069] In some embodiments, each R^z is selected from those depicted in **Table 1**, below.

[0070] As generally defined above, Ring Q is selected from benzo or a fused 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

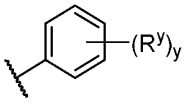
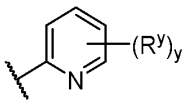
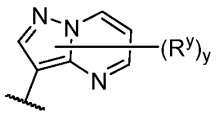
[0071] In some embodiments, Ring Q is benzo. In some embodiments, Ring Q is a fused 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

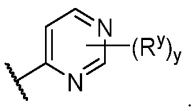
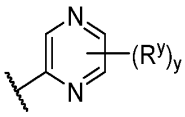
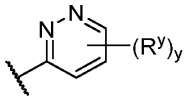
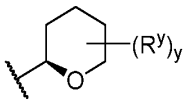
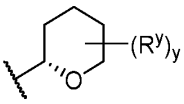
[0072] In some embodiments, Ring Q is  . In some embodiments, Ring Q is  . In some embodiments, Ring Q is  .

[0073] In some embodiments, each Ring Q is selected from those depicted in **Table 1**, below.

[0074] As generally defined above, Ring T is selected from phenyl, a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring T is further optionally substituted with 1-2 oxo groups;

[0075] In some embodiments, Ring T is from phenyl. In some embodiments, Ring T is a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring T is a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring T is further optionally substituted with 1-2 oxo groups.

[0076] In some embodiments, Ring T is  . In some embodiments, Ring T is  . In some embodiments, Ring T is  . In some embodiments, Ring T

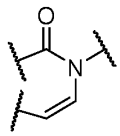
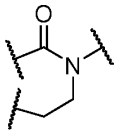
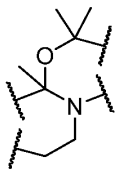
is  . In some embodiments, Ring T is  . In In some embodiments, Ring T is  . In some embodiments, Ring T is phenyl. In some embodiments, Ring T is  . In some embodiments, Ring T is  .

[0077] In some embodiments, Ring T is selected from those depicted in **Table 1**, below.

[0078] As generally defined above, L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -Cy^x-, -O-, -S-, -C(O)-, -C(S)-, -CR_2-, -CRF-, -CF_2-, -NR-, -N=CR-, -CR=CR-, or -$S(O)_2$-, wherein R of -CR_2-, -CRF-, -NR-, -N=CR-, or -CR=CR- can combine with R^x or R^y to form a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0079] In some embodiments, L^x is a covalent bond. In some embodiments, L^x is a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -Cy^x-, -O-, -S-, -C(O)-, -C(S)-, -CR_2-, -CRF-, -CF_2-, -NR-, -N=CR-, -CR=CR-, or -$S(O)_2$-. In some embodiments, R of -CR_2-, -CRF-, -NR-, -N=CR-, or -CR=CR- can combine with R^x or R^y to form a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0080] In some embodiments, L^x is -C(O)N(H)-. In some embodiments, L^x is -CH_2C(O)N(H)-.

[0081] In some embodiments, L^x combines with R^y to form  . In some embodiments, L^x combines with Ry to form  . In some embodiments, L^x combines with R^y and R^x to form  .

[0082] In some embodiments, Ring L^x is selected from those depicted in **Table 1**, below.

[0083] As generally defined above, -Cy^x- is an optionally substituted ring selected from a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein -Cy^x- is optionally substituted with 1-2 oxo groups.

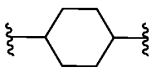
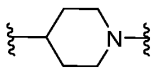
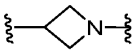
[0084] In some embodiments, -Cy^x- is an optionally substituted ring selected from a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, -Cy^x- is a 5 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, -Cy^x- is optionally substituted with 1-2 oxo groups.

[0085] In some embodiments, Ring -Cy^x- is selected from those depicted in **Table 1**, below.

[0086] As described above, X is a covalent bond or an optionally substituted bivalent ring selected from phenylenyl, a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0087]

[0088] In some embodiments, X is a covalent bond. In some embodiments, X is an optionally substituted phenylenyl. In some embodiments, X is an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, X is an optionally substituted 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0089] In some embodiments, X is  . In some embodiments, X is  . In some embodiments, X is  .

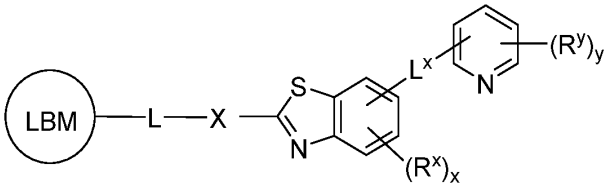
[0090] In some embodiments, X is selected from those depicted in **Table 1**, below.

[0091] As generally defined above, each x and y are independently 0, 1, 2, 3 or 4.

[0092] In some embodiments, each x and y are independently 0. In some embodiments, each x and y are independently 1. In some embodiments, each x and y are independently 2. In some embodiments, each x and y are independently 3. In some embodiments, each x and y are independently 4.

[0093] In some embodiments, each x and y are selected from those depicted in **Table 1**, below.

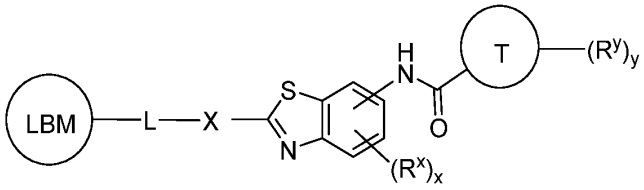
[0094] In some embodiments, the present invention provides a compound of formula **I-a**, wherein Ring Q is benzo and Ring T is pyridinyl as shown, to provide a compound of formula **I-a-1**:



I-a-1

or a pharmaceutically acceptable salt thereof, wherein each of LBM, L, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

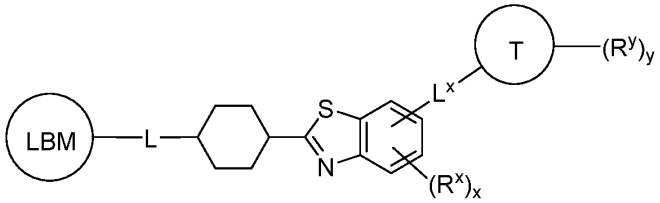
[0095] In some embodiments, the present invention provides a compound of formula **I-a**, wherein Ring Q is benzo and L^x is an amide as shown, to provide a compound of formula **I-a-2**:



I-a-2

or a pharmaceutically acceptable salt thereof, wherein each of LBM, L, X, R^x, R^y, Ring T, x, and y is as defined above and described in embodiments herein, both singly and in combination.

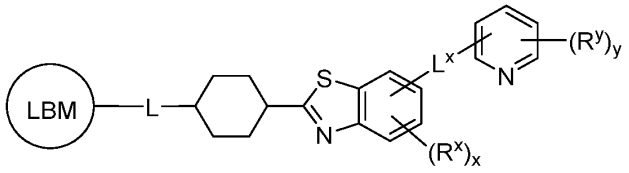
[0096] In some embodiments, the present invention provides a compound of formula **I-a**, wherein Ring Q is benzo and X is cyclohexyl as shown, to provide a compound of formula **I-a-3**:



I-a-3

or a pharmaceutically acceptable salt thereof, wherein each of LBM, L, R^x, R^y, Ring T, x, and y is as defined above and described in embodiments herein, both singly and in combination.

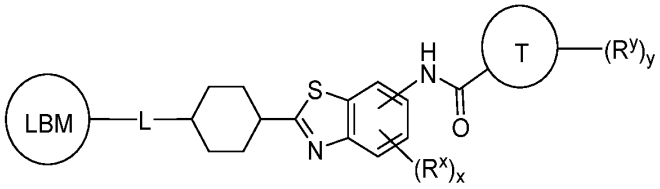
[0097] In some embodiments, the present invention provides a compound of formula **I-a**, wherein Ring Q is benzo, X is cyclohexyl, and Ring T is pyridinyl as shown, to provide a compound of formula **I-a-4**:



I-a-4

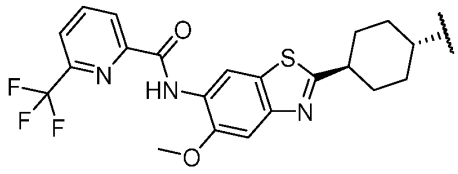
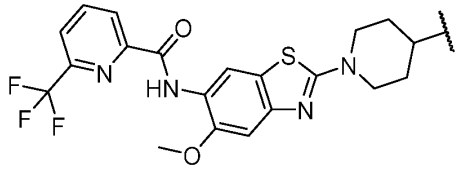
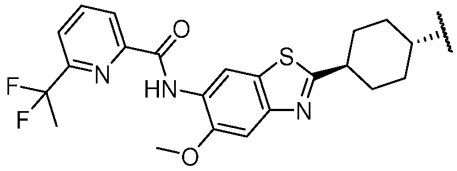
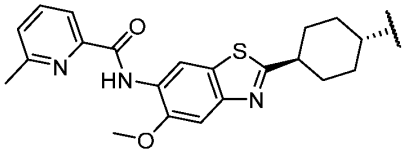
or a pharmaceutically acceptable salt thereof, wherein each of LBM, L, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

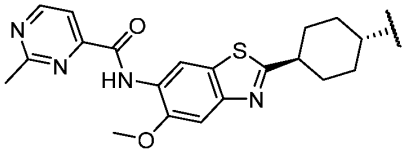
[0098] In some embodiments, the present invention provides a compound of formula **I-a**, wherein Ring Q is benzo, X is cyclohexyl, and L^x is an amide as shown, to provide a compound of formula **I-a-5**:



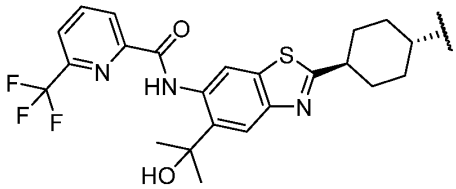
I-a-5

or a pharmaceutically acceptable salt thereof, wherein each of LBM, L, R^x, R^y, Ring T, x, and y is as defined above and described in embodiments herein, both singly and in combination.

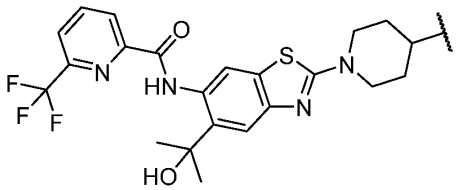
[0099] In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is



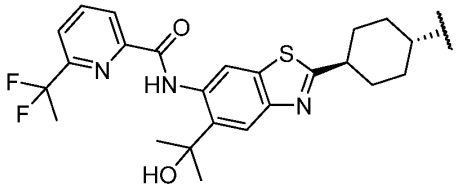
. In some embodiments, IRAK is



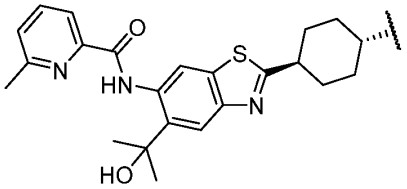
. In some embodiments, IRAK is



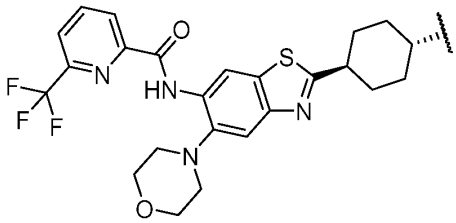
. In some embodiments, IRAK is



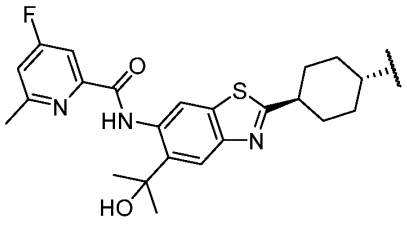
. In some embodiments, IRAK is



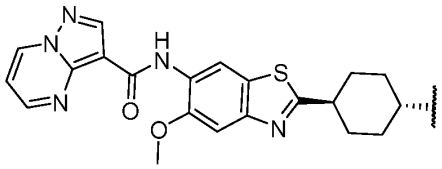
. In some embodiments, IRAK is



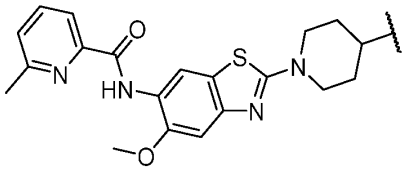
. In some embodiments, IRAK is



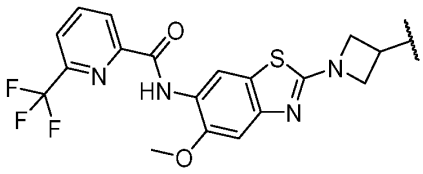
. In some embodiments, IRAK is



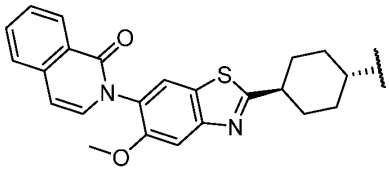
. In some embodiments, IRAK is



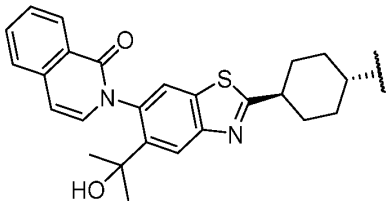
. In some embodiments, IRAK is



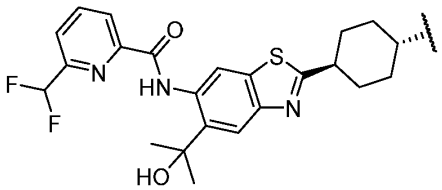
. In some embodiments, IRAK is



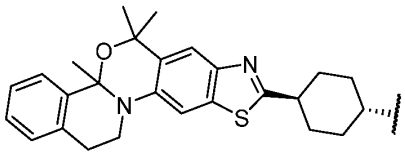
. In some embodiments, IRAK is



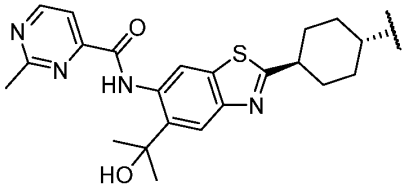
. In some embodiments, IRAK is



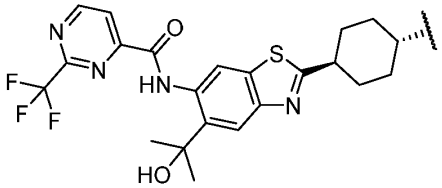
. In some embodiments, IRAK is



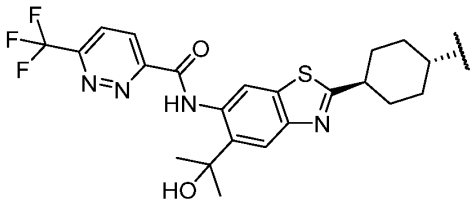
. In some embodiments, IRAK is



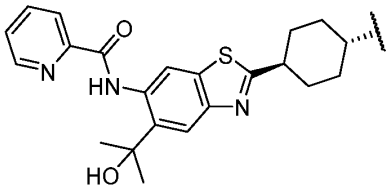
. In some embodiments, IRAK is



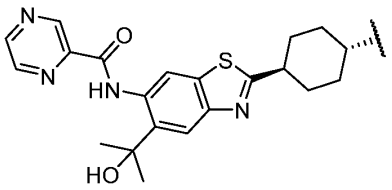
. In some embodiments, IRAK is



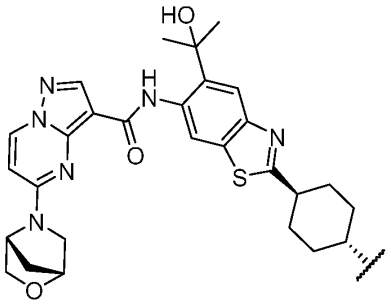
. In some embodiments, IRAK is



. In some embodiments, IRAK is



. In some embodiments, IRAK is



.

[00100] In some embodiments, IRAK is selected from those depicted in **Table 1**, below.

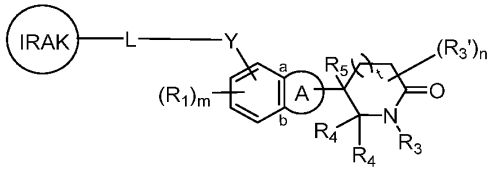
Ligase Binding Moiety (LBM)

[00101] In some embodiments, LBM is an E3 ligase ligand well known to one of ordinary skill in the art including those described in M. Toure, C. M. Crews, *Angew. Chem. Int. Ed.* 2016, *55*, 1966, T. Uehara *et al. Nature Chemical Biology* 2017, *13*, 675, WO 2017/176708, US 2017/0281784, WO 2017/161119, WO 2017/176957, WO 2017/176958, WO 2015/160845, US 2015/0291562, WO 2016/197032, WO 2016/105518, US 2018/0009779, WO 2017/007612, 2018/0134684, WO 2013/106643, US 2014/0356322, WO 2002/020740, US 2002/0068063, WO 2012/078559, US 2014/0302523, WO 2012/003281, US 2013/0190340, US 2016/0022642, WO 2014/063061, US 2015/0274738, WO 2016/118666, US 2016/0214972, WO 2016/149668, US 2016/0272639, WO 2016/169989, US 2018/0118733, WO 2016/197114, US 2018/0147202, WO 2017/011371, US 2017/0008904, WO 2017/011590, US 2017/0037004, WO 2017/079267, US 2017/0121321, WO 2017/117473, WO 2017/117474, WO 2013/106646, WO 2014/108452, WO 2017/197036, US 2019/0076540, WO 2017/197046, US 2019/0076542, WO 2017/197051, US 2019/0076539, WO 2017/197055, US 2019/0076541, and WO 2017/197056, the entirety of each of which is herein incorporated by reference.

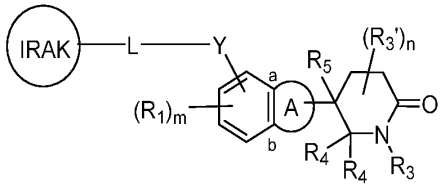
[00102] In certain embodiments, LBM is a cereblon (CRBN) E3 ubiquitin ligase binding moiety. In some embodiments, LBM is an IMiD-based cereblon E3 ubiquitin ligase binding moiety.

[00103] In some embodiments, an IMiD-based cereblon E3 ligase binding moiety, including those disclosed and described herein, includes thalidomide, lenalidomide, pomalidomide, avadomide (CC-122), iberdomide (CC-220), CC-92480, CC-885, CC-9009, and analogs thereof, and those IMiD-based cereblon ligands found in WO 2002059106, US 7,629,360, US 5,874,448, WO 2009145899, WO 2009042177, WO 1999047512, WO 2008039489, WO 2008115516, WO 2009139880, US 20110196150, WO 2008027542, WO 199854170, WO 199946258, and WO 2014018866, the contents of each of which is herein incorporated by reference. The IMiD-based IRAK degraders described and disclosed herein specifically degrade (a) an IRAK protein and (b) either (i) ikaros (IKZF1) (Ensembl Gene ID: ENG00000185811), (ii) aiolos (IKZF3) (Ensembl Gene ID: ENSG00000161405), or (iii) both ikaros and aiolos.

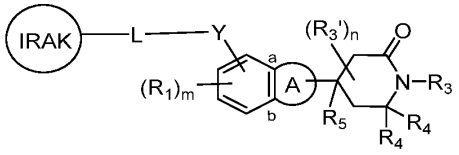
[00104] In some embodiments, the present invention provides a compound of Formula **I**, wherein LBM is an IMiD-based cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-oo-1**, **I-oo-2**, **I-oo-3**, **I-oo-4**, **I-oo-5**, **I-oo-6**, **I-oo-7**, **I-oo-8**, **I-oo-9**, or **I-oo-10** respectively:



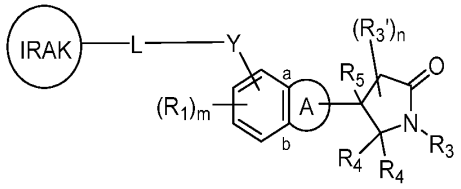
I-oo-1



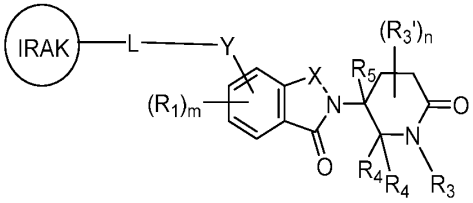
I-oo-2



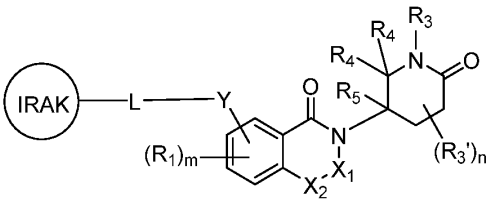
I-oo-3



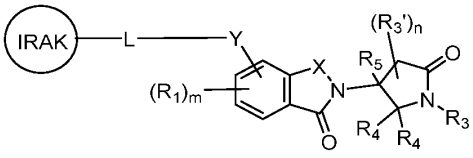
I-oo-4



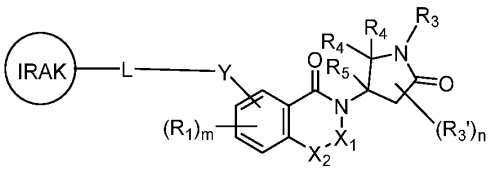
I-oo-5



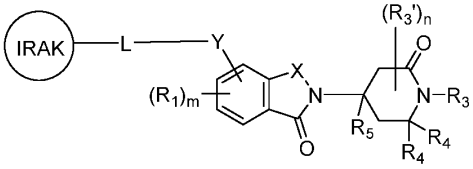
I-oo-6



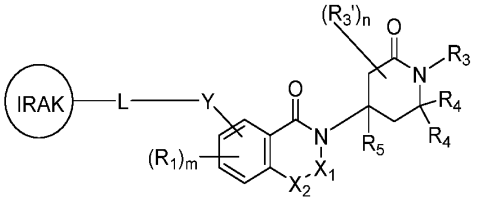
I-oo-7



I-oo-8

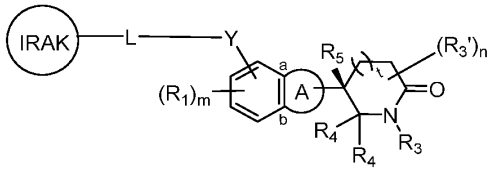


I-oo-9

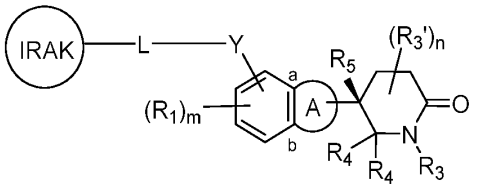


I-oo-10

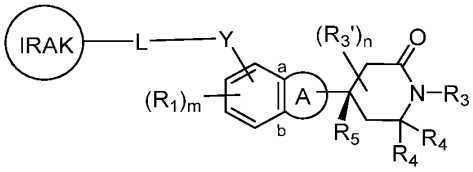
or a compound of formula **I-oo′-1**, **I-oo′-2**, **I-oo′-3**, **I-oo′-4**, **I-oo′-5**, **I-oo′-6**, **I-oo′-7**, **I-oo′-8**, **I-oo′-9**, or **I-oo′-10** respectively:

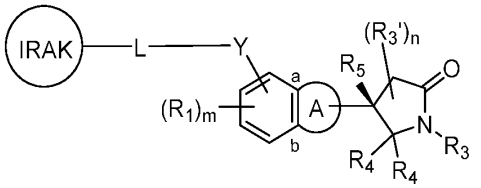


I-oo′-1

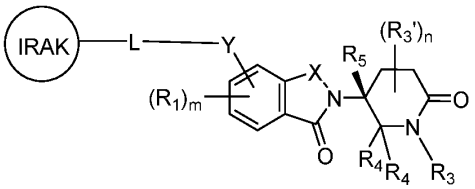


I-oo′-2

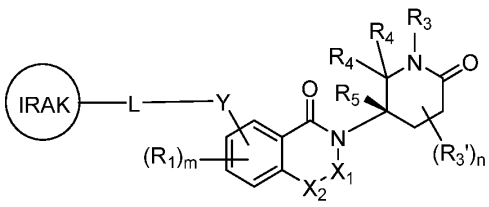




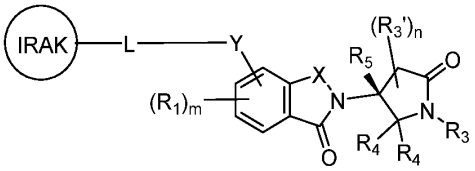
I-oo′-3



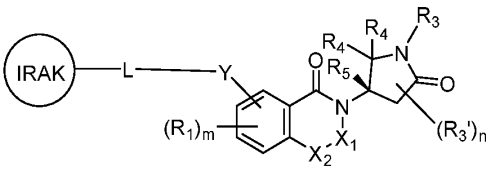
I-oo′-4



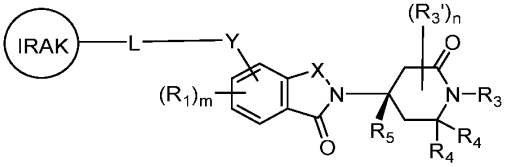
I-oo′-5



I-oo′-6



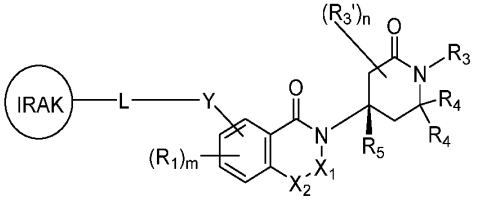
I-oo′-7



I-oo′-8

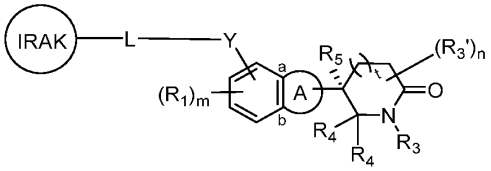
I-oo′-9

I-oo′-10

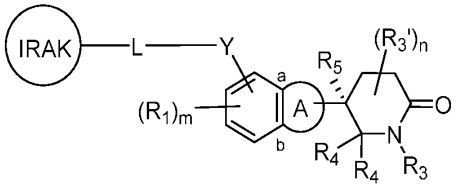


or a compound of formula **I-oo″-1**, **I-oo″-2**, **I-oo″-3**, **I-oo″-4**, **I-oo″-5**, **I-oo″-6**, **I-oo″-7**, **I-oo″-8**, **I-oo″-9**, or **I-oo″-10** respectively:

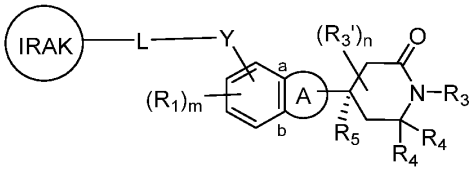
I-oo″-1



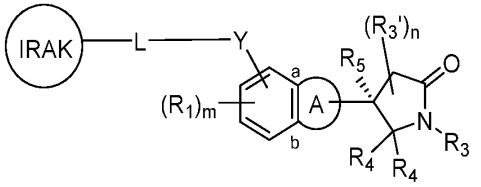
I-oo″-2

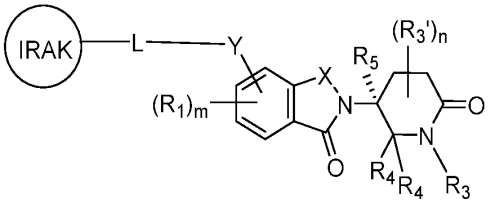


I-oo″-3

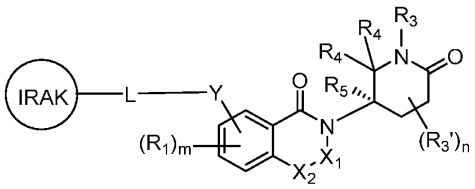


I-oo″-4

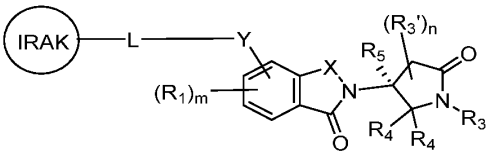




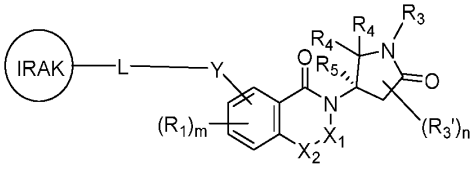
I-oo″-5



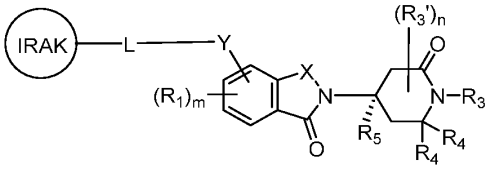
I-oo″-6



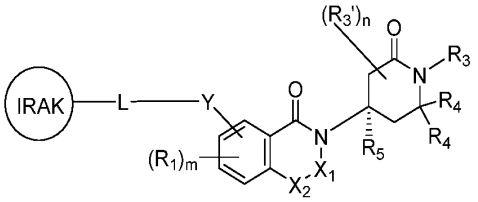
I-oo″-7



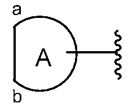
I-oo″-8



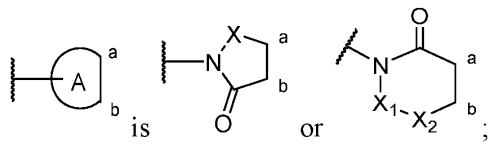
I-oo″-9



I-oo″-10

or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein each of the variables  , X, X_1, X_2, Y, R_1, R_3, R_3', R_4, R_5, t, m and n is as defined and described in WO 2017/007612 and US 2018/0134684, the entirety of each of which is herein incorporated by reference.

[00105] Accordingly in some embodiments, the present invention provides a compound of formula **I-oo-1**, **I-oo-2**, **I-oo-3**, **I-oo-4**, **I-oo-5**, **I-oo-6**, **I-oo-7**, **I-oo-8**, **I-oo-9**, **I-oo-10**, **I-oo′-1**, **I-oo′-2**, **I-oo′-3**, **I-oo′-4**, **I-oo′-5**, **I-oo′-6**, **I-oo′-7**, **I-oo′-8**, **I-oo′-9**, **I-oo′-10**, **I-oo″-1**, **I-oo″-2**, **I-oo″-3**, **I-oo″-4**, **I-oo″-5**, **I-oo″-6**, **I-oo″-7**, **I-oo″-8**, **I-oo″-9**, or **I-oo″-10**, or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein:



is or ;

Y is a bond, Y_1, O, NH, NR_2, C(O)O, OC(O), C(O)NR_2′, NR_2′C(O), Y_1—O, Y_1—NH, Y_1—NR_2, Y_1—C(O), Y_1—C(O)O, Y_1—OC(O), Y_1—C(O)NR_2′, or Y_1—NR_2′C(O), wherein Y_1 is C_1-C_6 alkylene,

C_2-C_6 alkenylene, or C_2-C_6 alkynylene;

X is C(O) or $C(R_3)_2$;

X_1-X_2 is $C(R_3)$=N or $C(R_3)_2$—$C(R_3)_2$;

each R_1 is independently halogen, nitro, NH_2, OH, C(O)OH, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

R_2 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C(O)—C_1-C_6 alkyl, C(O)—C_2-C_6 alkenyl, C(O)—C_3-C_8 cycloalkyl, or C(O)-3- to 8-membered heterocycloalkyl, and R_2 is optionally substituted with one or more of halogen, $N(R_a)_2$, $NHC(O)R_a$, $NHC(O)OR_a$, OR_b, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each of the C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more of halogen, NH_2, CN, nitro, OH, C(O)OH, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkoxy;

R_2' is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, or 3- to 8-membered heterocycloalkyl, and R_2', when not being H, is optionally substituted with one or more of halogen, $N(R_a)_2$, $NHC(O)R_a$, $NHC(O)OR_a$, OR_b, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each of the C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more of halogen, NH_2, CN, nitro, OH, C(O)OH, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkoxy;

each R_3 is independently H or C_1-C_3 alkyl optionally substituted with C_6-C_{10} aryl or 5- to 10-membered heteroaryl;

each R_3' is independently C_1-C_3 alkyl;

each R_4 is independently H or C_1-C_3 alkyl; or two R_4, together with the carbon atom to which they are attached, form C(O), a C_3-C_6 carbocycle, or a 4-, 5-, or 6-membered heterocycle comprising 1 or 2 heteroatoms selected from N and O;

R_5 is H, C_1-C_3 alkyl, F, or Cl;

each R_a independently is H or C_1-C_6 alkyl;

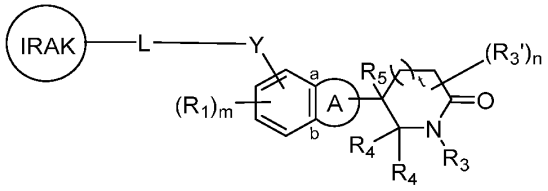
R_b is H or tosyl;

t is 0 or 1;

m is 0, 1, 2 or 3; and

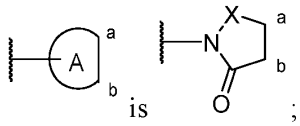
n is 0, 1 or 2.

[00106] In certain aspects, the present invention provides a compound of Formula **I**, wherein LBM is an IMID-based cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-oo-1**:



I-oo-1

or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein:



;

Y is a bond;

X is C(O) or CH_2;

each R_1 is independently hydrogen, halogen, C_1-C_4 alkyl, or C_1-C_4 alkoxy;

R_3 is hydrogen;

two R_4, together with the carbon atom to which they are attached, form C(O);

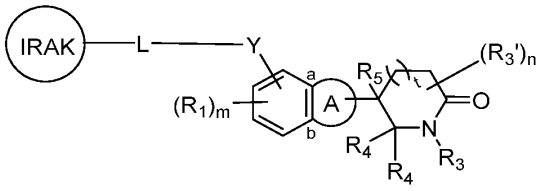
R_5 is hydrogen or C_1-C_3 alkyl;

t is 1;

m is 0, 1, 2, 3, or 4; and

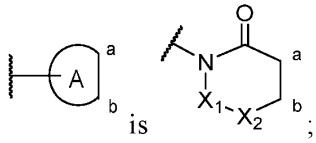
n is 0.

[00107] In certain aspects, the present invention provides a compound of Formula **I**, wherein LBM is an IMID-based cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-oo-1**:



I-oo-1

or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein:



;

Y is a bond;

X_1-X_2 is C(H)=N, C(C_1-C_4 alkyl)=N, or C(C_1-C_4 haloalkyl);

each R_1 is independently hydrogen, halogen, -NH_2, -OH, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkoxy;

R_3 is hydrogen;

two R_4, together with the carbon atom to which they are attached, form C(O);

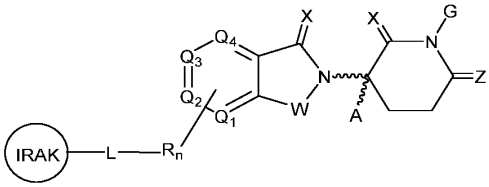
R_5 is hydrogen or C_1-C_3 alkyl;

t is 1;

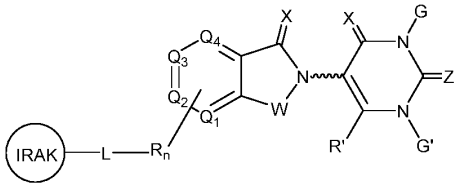
m is 0, 1, 2 or 3; and

n is 0.

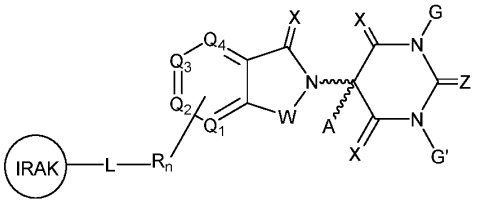
[00108] In some embodiments, the present invention provides a compound of Formula **I**, wherein LBM is an IMID-based cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-pp-1**, **I-pp-2**, **I-pp-3**, **I-pp-4**, **I-pp-5**, or **I-pp-6** respectively:



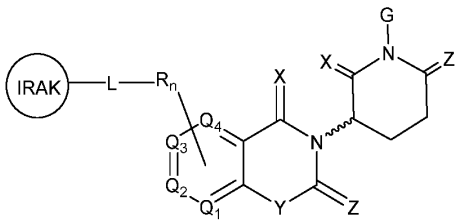
I-pp-1



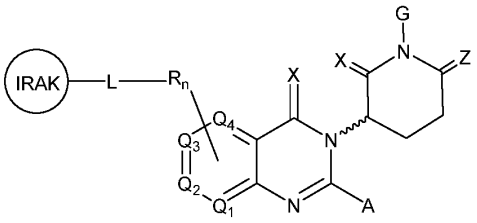
I-pp-2



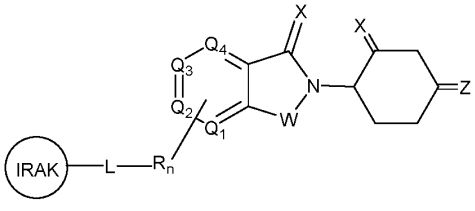
I-pp-3



I-pp-4



I-pp-5

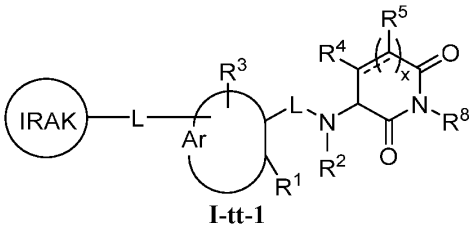


I-pp-6

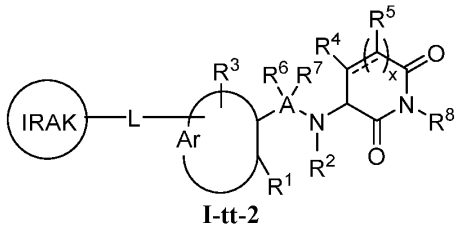
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein each of the variables A, G, G', Q_1, Q_2, Q_3, Q_4, R, R', W, X, Y, Z, ~~~,

and n is as defined and described in WO 2016/197114 and US 2018/0147202, the entirety of each of which is herein incorporated by reference.

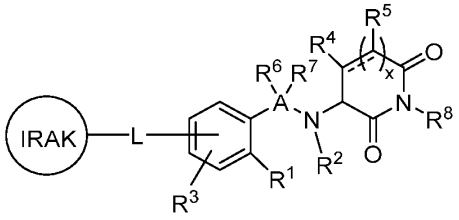
[00109] In certain embodiments, the present invention provides a compound of formula **I**, wherein LBM is an IMID-based E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-tt-1**, **I-tt-2**, **I-tt-3**, **I-tt-4**, **I-tt-5**, **I-tt-6**, **I-tt-7**, or **I-tt-8**:



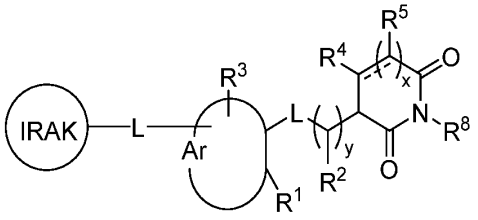
I-tt-1



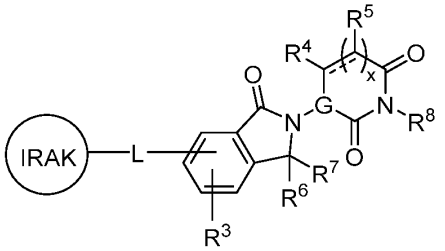
I-tt-2



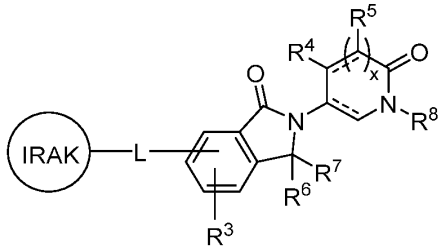
I-tt-3



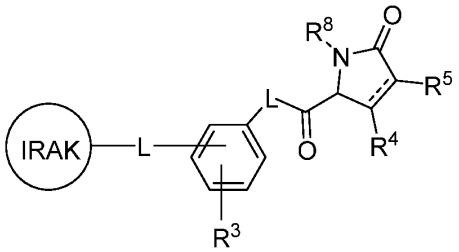
I-tt-4



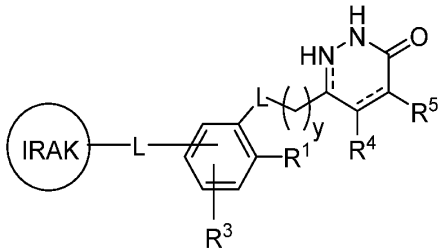
I-tt-5



I-tt-6



I-tt-7

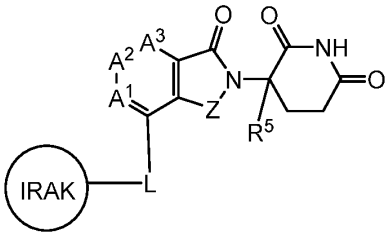


I-tt-8

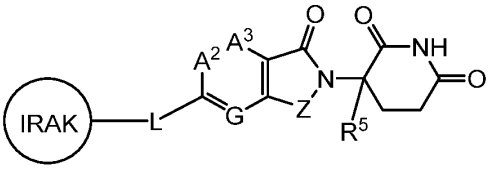
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein each of the variables Ar, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, A, L, x, y, and ═ is as described and defined in WO 2017/161119, the entirety of each of which is herein incorporated by

reference.

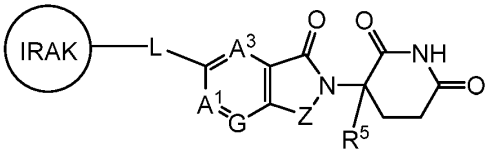
[00110] In certain embodiments, the present invention provides a compound of Formula **I**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-zz-1**, **I-zz-2**, **I-zz-3**, **I-zz-4**, or **I-zz-5**, respectively:



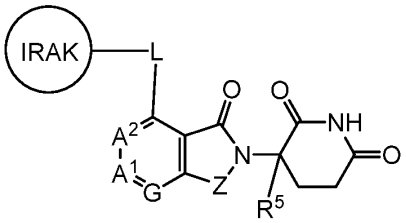
I-zz-1



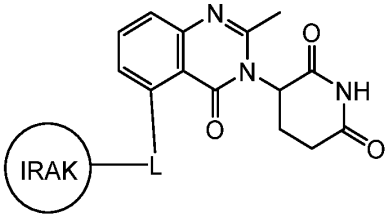
I-zz-2



I-zz-3



I-zz-4

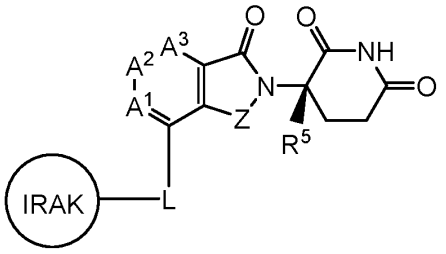


I-zz-5

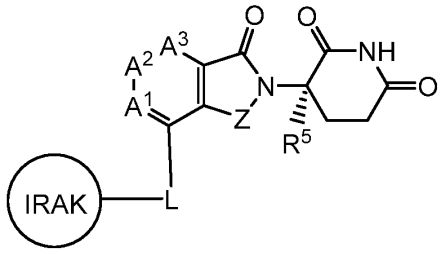
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in

embodiments herein, and wherein each of the variables A^1, A^2, A^3, R^5, G and Z is as defined and described in WO 2017/176958.

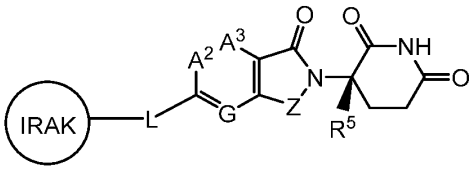
[00111] In certain embodiments, the present invention provides a compound of Formula **I**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-zz′-1**, **I-zz″-1**, **I-zz′-2**, **I-zz′-2**, **I-zz′-3**, **I-zz″-3**, **I-zz′-4**, **I-zz″-4**, **I-zz′-5** or **I-zz″-5** respectively:



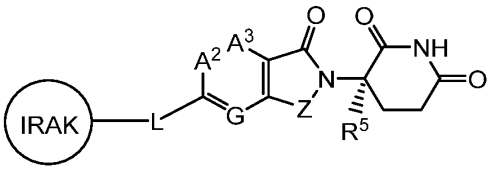
I-zz′-1



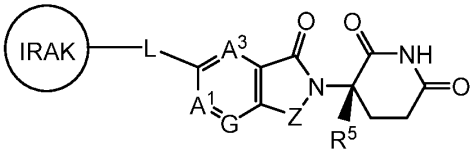
I-zz″-1



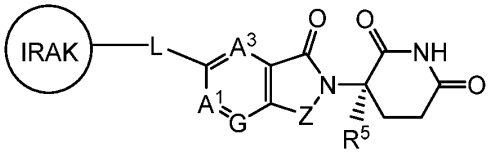
I-zz′-2



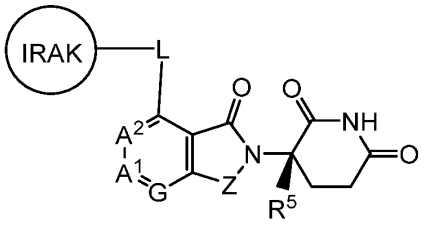
I-zz″-2



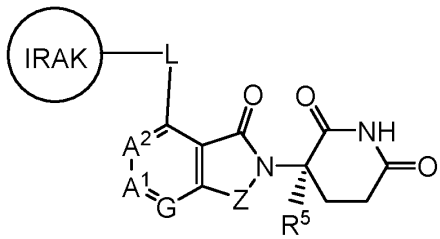
I-zz′-3



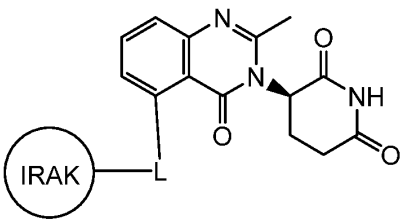
I-zz″-3

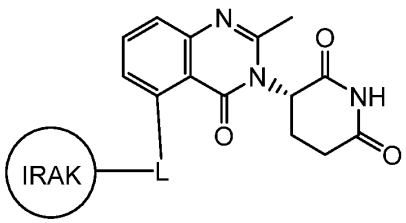


I-zz′-4



I-zz″-4

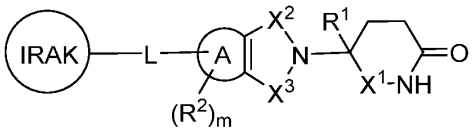




I-zz′-5 **I-zz″-5**

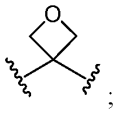
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein each of the variables A^1, A^2, A^3, R^5, G and Z is as defined and described in WO 2017/176958, the entirety of which is herein incorporated by reference.

[00112] In certain embodiments, the present invention provides a compound of Formula **I**, wherein LBM is an IMiD-based cereblon E3 ubiquitin ligase binding moiety, thereby forming a compound of formula **I-ccc-1**:



I-ccc-1

or a pharmaceutically acceptable salt thereof, wherein L and IRAK is as defined above and described in embodiments herein, and wherein:

each of X^1, X^2, and X^3 is independently a bivalent moiety selected from a covalent bond, $–CH_2–$, –C(O)–, –C(S)–, and  ;

R^1 is hydrogen, deuterium, halogen, –CN, –OR, –SR, $–S(O)R$, $–S(O)_2R$, $–NR_2$, or an optionally substituted C_{1-4} aliphatic;

each of R^2 is independently hydrogen, R^6, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $–N(R)S(O)_2R$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

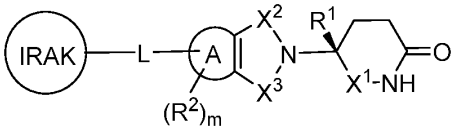
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and

sulfur;

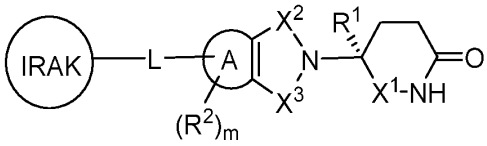
Ring A is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur; and

m is 0, 1, 2, 3 or 4.

[00113] In certain embodiments, the present invention provides a compound of formula **I-ccc-1**, wherein LBM is an IMID-based cereblon E3 ubiquitin ligase (cereblon) binding moiety thereby forming a compound of formula **I-ccc′-1** or **I-ccc′′-1**:



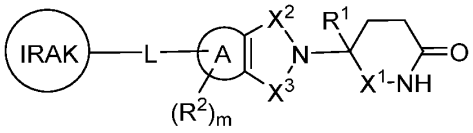
I-ccc′-1



I-ccc′′-1

or a pharmaceutically acceptable salt thereof, wherein IRAK, L, Ring A, X^1, X^2, X^3, R^1, R^2 and m are as described above.

[00114] In certain aspects, the present invention provides a compound of Formula **I**, wherein LBM is a IMID-based cereblon E3 ubiquitin ligase binding moiety thereby forming a compound of formula **I-ccc-1**:



I-ccc-1

or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein:

X^1 is –C(O)–;

X^2 is –C(O)–;

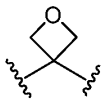
X^3 is $–CH_2–$ or –C(O)–;

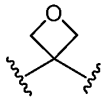
R^1 is hydrogen or C_{1-4} aliphatic;

each of R^2 is independently hydrogen, halogen, C_{1-4} aliphatic or $–OC_{1-4}$ aliphatic;

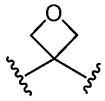
Ring A is benzo; and

m is 0, 1, 2, 3 or 4.

[00115] As defined above and described herein, each of X^1, X^2, and X^3 is independently a bivalent moiety selected from a covalent bond, $-CH_2-$, $-C(O)-$, $-C(S)-$, and  .

[00116] In some embodiments, X^1 is a covalent bond, $-CH_2-$, $-C(O)-$, $-C(S)-$, or  .

[00117] In some embodiments, X^1 is selected from those depicted in **Table 1**, below.

[00118] In some embodiments, X^2 is a covalent bond, $-CH_2-$, $-C(O)-$, $-C(S)-$, or  .

[00119] In some embodiments, X^2 is selected from those depicted in **Table 1**, below.

[00120] In some embodiments, X^3 is a covalent bond, $-CH_2-$, $-C(O)-$, $-C(S)-$, or  .

[00121] In some embodiments, X^3 is selected from those depicted in **Table 1**, below.

[00122] As defined above and described herein, R^1 is hydrogen, deuterium, halogen, –CN, –OR, –SR, $-S(O)R$, $-S(O)_2R$, $-NR_2$, or an optionally substituted C_{1-4} aliphatic.

[00123] In some embodiments, R^1 is hydrogen, deuterium, halogen, –CN, –OR, –SR, $-S(O)R$, $-S(O)_2R$, $-NR_2$, or an optionally substituted C_{1-4} aliphatic.

[00124] In some embodiments, R^1 is selected from those depicted in **Table 1**, below.

[00125] As defined above and described herein, each of R^2 is independently hydrogen, R^6, halogen, –CN, $-NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$.

[00126] In some embodiments, R^2 is hydrogen, R^6, halogen, –CN, $-NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$.

[00127] In some embodiments, R^2 is selected from those depicted in **Table 1**, below.

[00128] As defined above and described herein, each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic

ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00129] In some embodiments, R^6 is an optionally substituted C_{1-6} aliphatic group. In some embodiments, R^6 is an optionally substituted phenyl. In some embodiments, R^6 is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^6 is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00130] In some embodiments, R^6 is selected from those depicted in **Table 1**, below.

[00131] As defined above and described herein, Ring A is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur.

[00132] In some embodiments Ring A is a fused 6-membered aryl containing 0-2 nitrogen atoms. In some embodiments Ring A is a fused 5 to 7-membered partially saturated carbocyclyl. In some embodiments Ring A is a fused 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur. In some embodiments Ring A is a fused 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur.

[00133] In some embodiments, Ring A is a fused phenyl or benzo.

[00134] In some embodiments, Ring A is selected from those depicted in **Table 1**, below.

[00135] As defined above and described herein, m is 0, 1, 2, 3 or 4.

[00136] In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4.

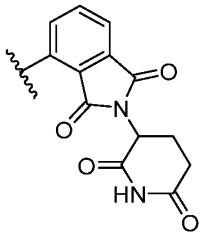
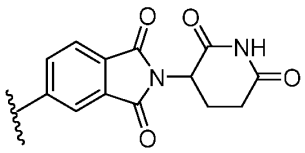
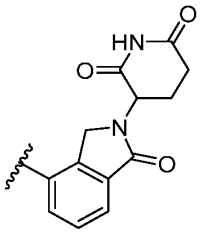
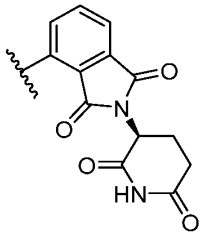
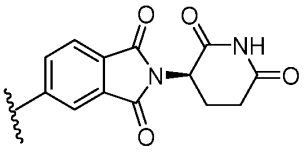
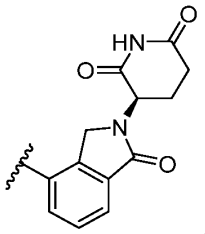
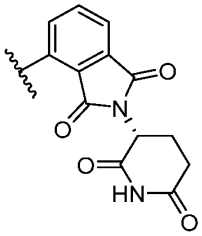
[00137] In some embodiments, m is selected from those depicted in **Table 1**, below.

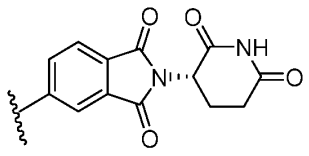
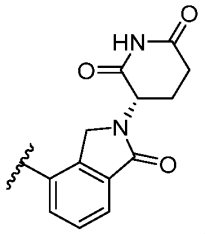
[00138] As defined above and described herein, each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or: two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

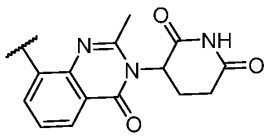
[00139] In some embodiments, R is hydrogen. In some embodiments, R is phenyl. In some embodiments, R is a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms

independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

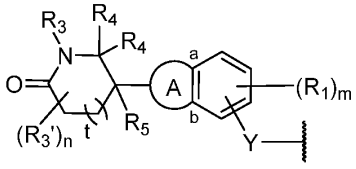
[00140] In some embodiments, R is selected from those depicted in **Table 1**, below.

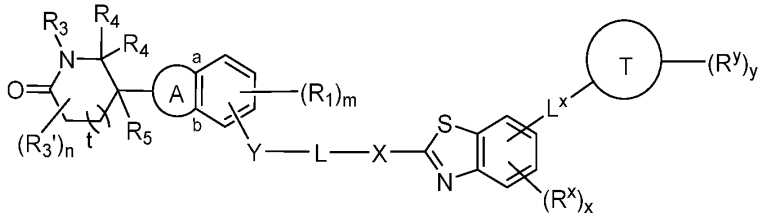
[00141] In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is  . In some embodiments, LBM is .

embodiments, LBM is  . In some embodiments, LBM is  .

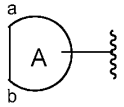
In some embodiments, LBM is  .

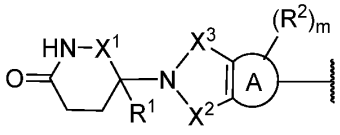
[00142] In some embodiments, LBM is selected from those in **Table 1** below.

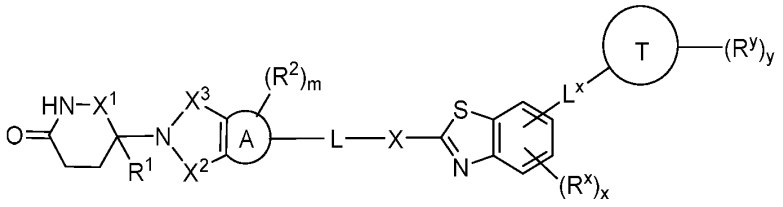
[00143] In some embodiments, the present invention provides a compound of formula **I-a**, wherein Ring Q is benzo and LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-6**:



I-a-6

or a pharmaceutically acceptable salt thereof, wherein each of variables  , Y, R_1, R_3, R_3', R_4, R_5, t, m, n, Ring T, L, L^x, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

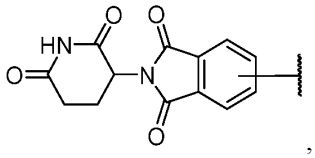
[00144] In some embodiments, the present invention provides a compound of formula **I-a**, wherein Ring Q is benzo and LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-7**:



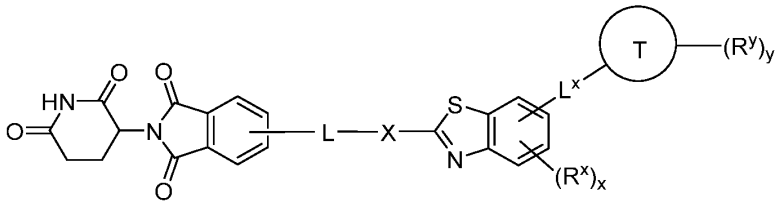
I-a-7

or a pharmaceutically acceptable salt thereof, wherein each of variables X^1, X^2, X^3, R^1, R^2, Ring A, m, Ring T, L, L^x, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

[00145] In some embodiments, the present invention provides a compound of formula **I-a**, wherein



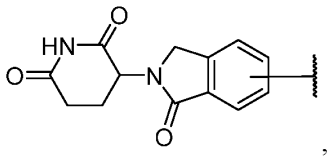
Ring Q is benzo and LBM is CRBN E3 ubiquitin ligase binding moiety , thereby providing a compound of formula **I-a-8**:



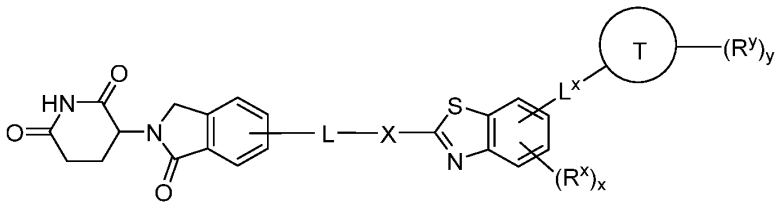
I-a-8

or a pharmaceutically acceptable salt thereof, wherein each of Ring T, L, L^x, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

[00146] In some embodiments, the present invention provides a compound of formula **I-a**, wherein

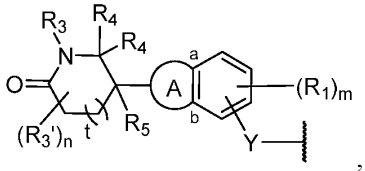


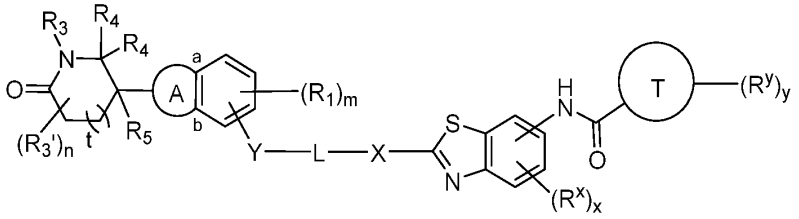
Ring Q is benzo and LBM is CRBN E3 ubiquitin ligase binding moiety , thereby providing a compound of formula **I-a-9**:



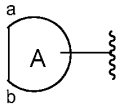
I-a-9

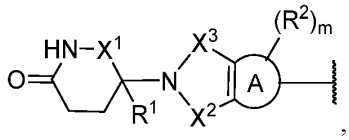
or a pharmaceutically acceptable salt thereof, wherein each of Ring T, L, L^x, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

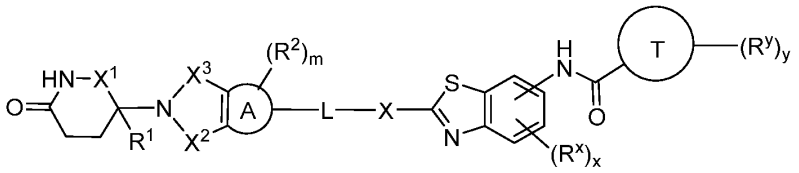
[00147] In some embodiments, the present invention provides a compound of formula **I-a**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-10**:



I-a-10

or a pharmaceutically acceptable salt thereof, wherein each of variables  , Y, R_1, R_3, R_3', R_4, R_5, t, m, n, Ring T, L, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

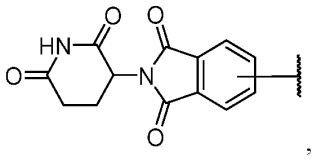
[00148] In some embodiments, the present invention provides a compound of formula **I-a-2**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-11**:

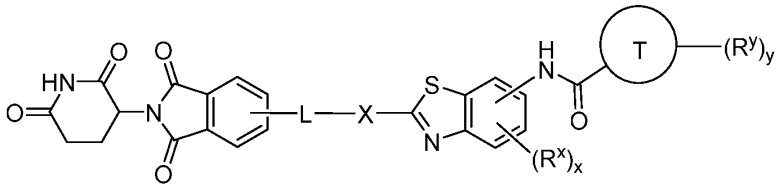


I-a-11

or a pharmaceutically acceptable salt thereof, wherein each of variables X^1, X^2, X^3, R^1, R^2, Ring A, m, Ring T, L, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

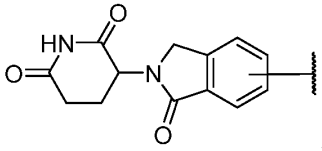
[00149] In some embodiments, the present invention provides a compound of formula **I-a-2**, wherein

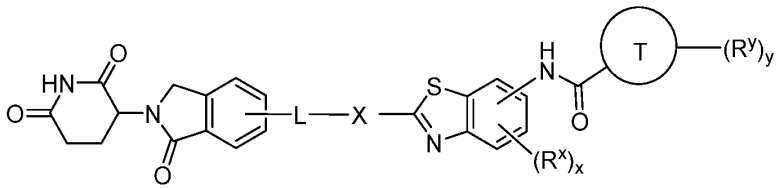
LBM is CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-12**:



I-a-12

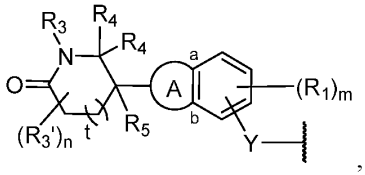
or a pharmaceutically acceptable salt thereof, wherein each of Ring T, L, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

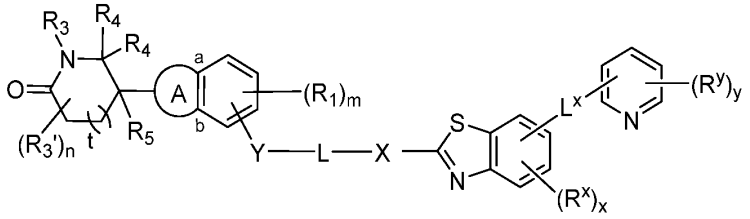
[00150] In some embodiments, the present invention provides a compound of formula **I-a-2**, wherein LBM is CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-13**:



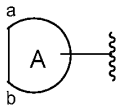
I-a-13

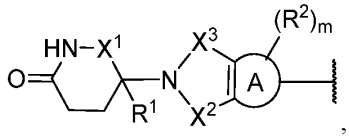
or a pharmaceutically acceptable salt thereof, wherein each of Ring T, L, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

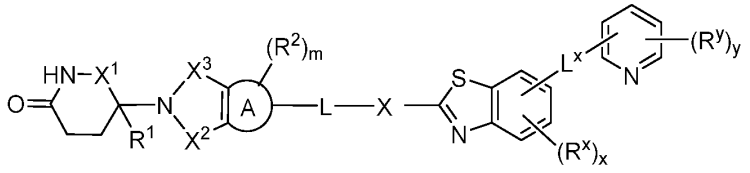
[00151] In some embodiments, the present invention provides a compound of formula **I-a-1**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-14**:



I-a-14

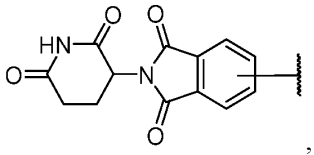
or a pharmaceutically acceptable salt thereof, wherein each of variables  , Y, R_1, R_3, R_3', R_4, R_5, t, m, n, L, L^x, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

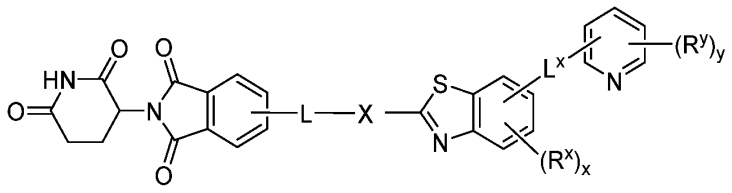
[00152] In some embodiments, the present invention provides a compound of formula **I-a-1**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-15**:



I-a-15

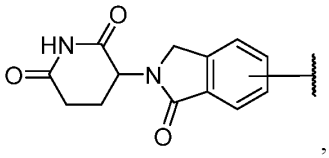
or a pharmaceutically acceptable salt thereof, wherein each of variables X^1, X^2, X^3, R^1, R^2, Ring A, m, L, L^x, X, R^x, R^y, x, and y is as as defined above and described in embodiments herein, both singly and in combination.

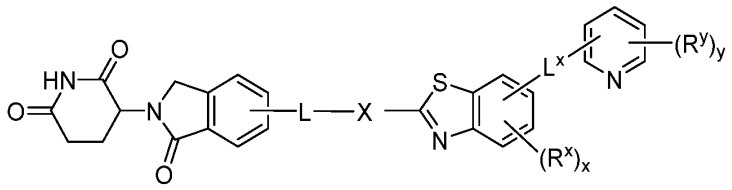
[00153] In some embodiments, the present invention provides a compound of formula **I-a-1**, wherein LBM is CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-16**:



I-a-16

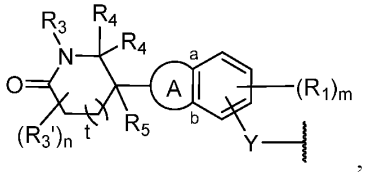
or a pharmaceutically acceptable salt thereof, wherein each of L, L^x, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

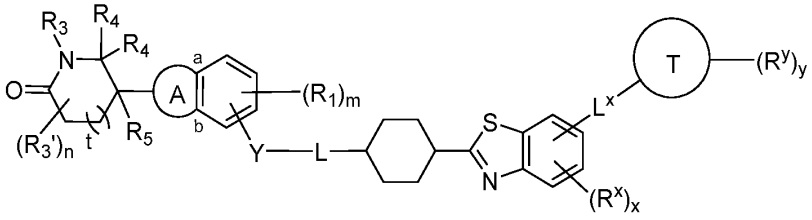
[00154] In some embodiments, the present invention provides a compound of formula **I-a-1**, wherein LBM is CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-17**:



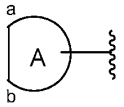
I-a-17

or a pharmaceutically acceptable salt thereof, wherein each of L, L^x, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

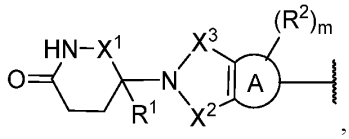
[00155] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-18**:



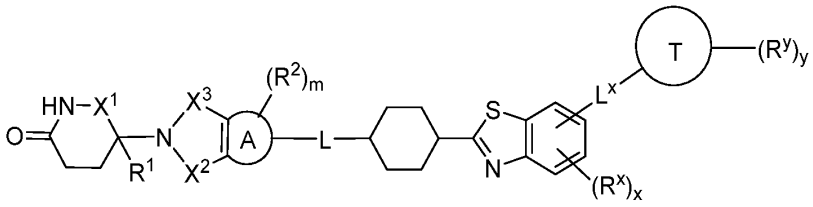
I-a-18



or a pharmaceutically acceptable salt thereof, wherein each of variables , Y, R_1, R_3, R_3', R_4, R_5, t, m, n, Ring T, L, L^x, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

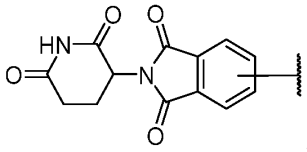
[00156] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety 

, thereby providing a compound of formula **I-a-19**:

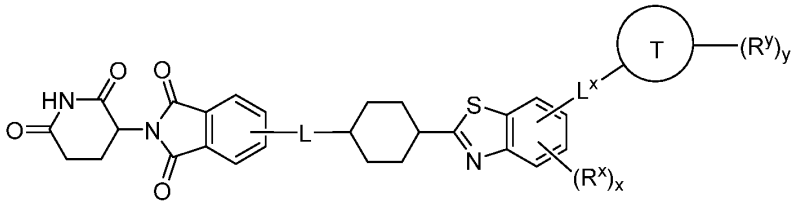


I-a-19

or a pharmaceutically acceptable salt thereof, wherein each of variables X^1, X^2, X^3, R^1, R^2, Ring A, m, Ring T, L, L^x, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

[00157] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein LBM is CRBN E3 ubiquitin ligase binding moiety 

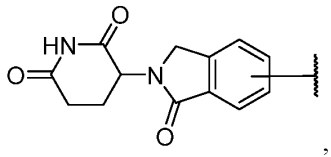
, thereby providing a compound of formula **I-a-20**:

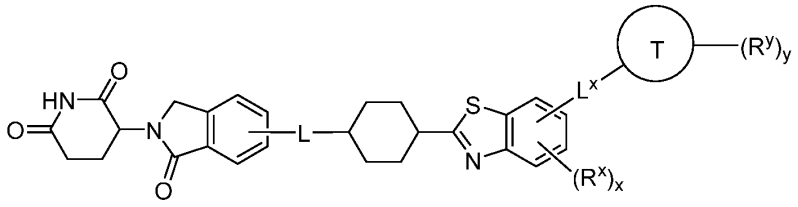


I-a-20

or a pharmaceutically acceptable salt thereof, wherein each of Ring T, L, L^x, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

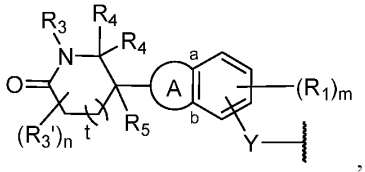
[00158] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein

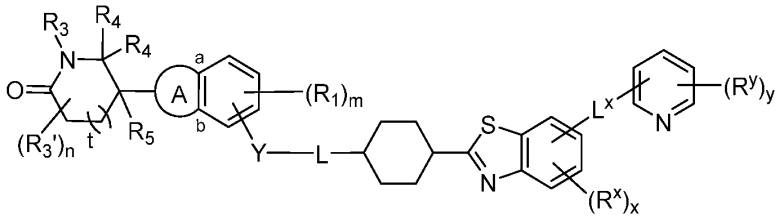
LBM is CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-21**:



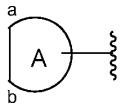
I-a-21

or a pharmaceutically acceptable salt thereof, wherein each of Ring T, L, L^x, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

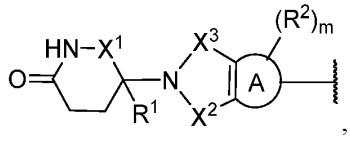
[00159] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-22**:

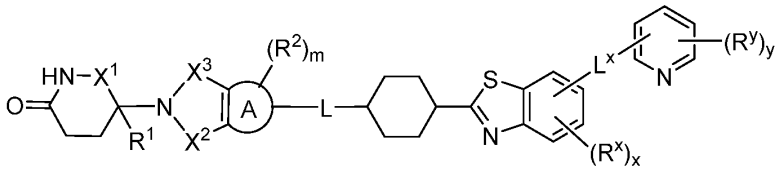


I-a-22

or a pharmaceutically acceptable salt thereof, wherein each of variables  , Y, R_1, R_3, R_3', R_4, R_5, t, m, n, L, L^x, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

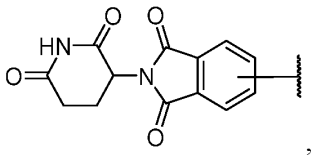
[00160] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein

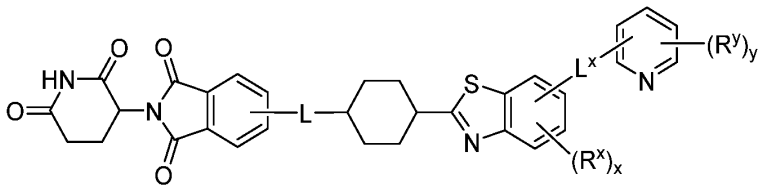
LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-23**:



I-a-23

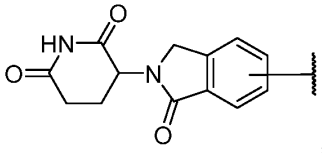
or a pharmaceutically acceptable salt thereof, wherein each of variables X^1, X^2, X^3, R^1, R^2, Ring A, m, L, L^x, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

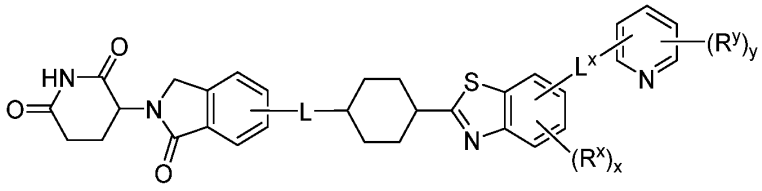
[00161] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein LBM is CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-24**:



I-a-24

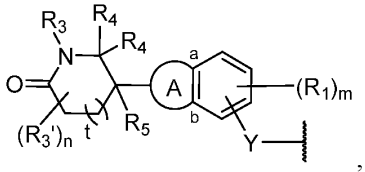
or a pharmaceutically acceptable salt thereof, wherein each of L, L^x, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

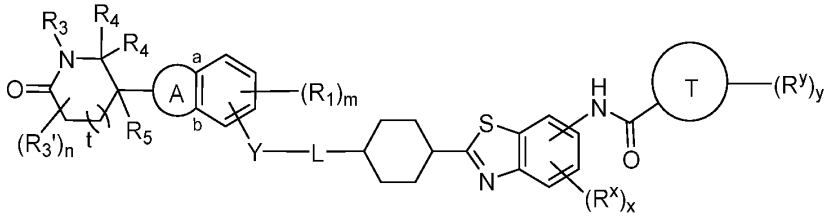
[00162] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein LBM is CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-25**:



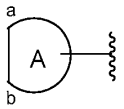
I-a-25

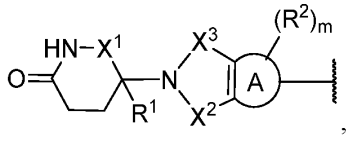
or a pharmaceutically acceptable salt thereof, wherein each of L, L^x, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

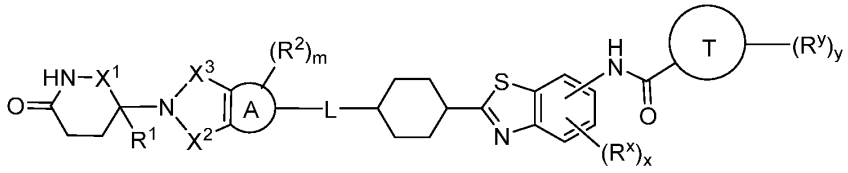
[00163] In some embodiments, the present invention provides a compound of formula **I-a-5**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-26**:



I-a-26

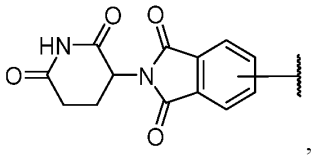
or a pharmaceutically acceptable salt thereof, wherein each of variables  , Y, R_1, R_3, R_3', R_4, R_5, t, m, n, Ring T, L, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

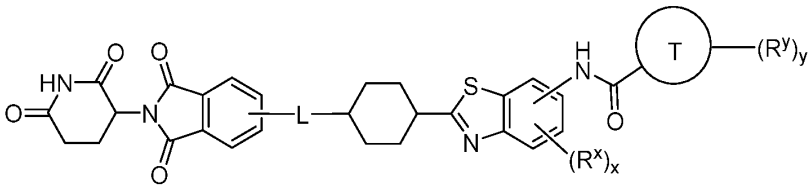
[00164] In some embodiments, the present invention provides a compound of formula **I-a-5**, wherein LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-27**:



I-a-27

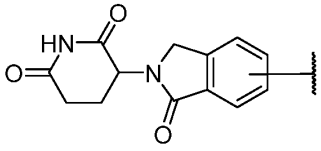
or a pharmaceutically acceptable salt thereof, wherein each of variables X^1, X^2, X^3, R^1, R^2, Ring A, m, Ring T, L, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

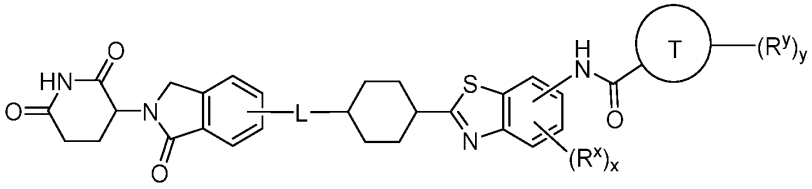
[00165] In some embodiments, the present invention provides a compound of formula **I-a-5**, wherein LBM is CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-28**:



I-a-28

or a pharmaceutically acceptable salt thereof, wherein each of Ring T, L, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

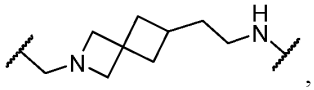
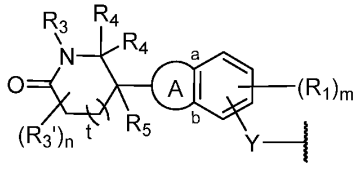
[00166] In some embodiments, the present invention provides a compound of formula **I-a-5**, wherein LBM is CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-29**:

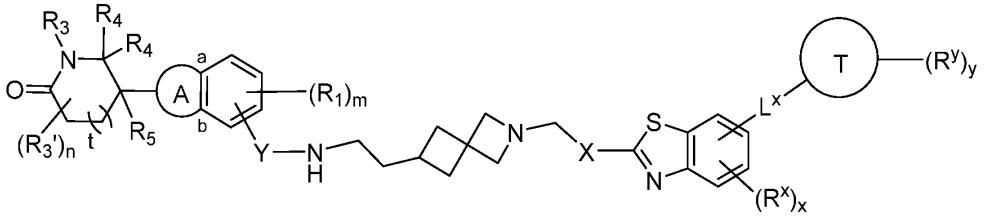


I-a-29

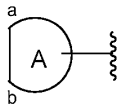
or a pharmaceutically acceptable salt thereof, wherein each of Ring T, L, R^x, R^y, x, and y is as defined above

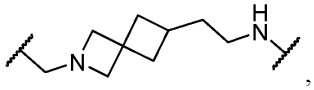
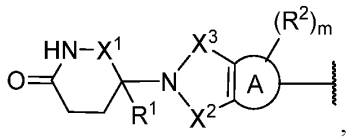
and described in embodiments herein, both singly and in combination.

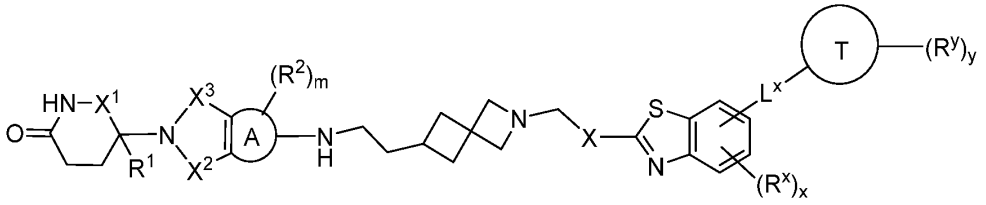
[00167] In some embodiments, the present invention provides a compound of formula **I-a**, wherein Ring Q is benzo, L is  , and LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-30**:



I-a-30

or a pharmaceutically acceptable salt thereof, wherein each of variables  , Y, R_1, R_3, R_3', R_4, R_5, t, m, n, Ring T, L^x, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

[00168] In some embodiments, the present invention provides a compound of formula **I-a**, wherein Ring Q is benzo, L is  , and LBM is an IMID-based CRBN E3 ubiquitin ligase binding moiety  , thereby providing a compound of formula **I-a-31**:



I-a-31

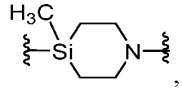
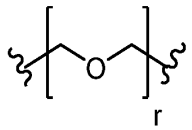
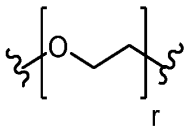
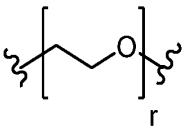
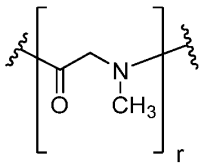
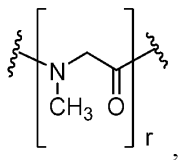
or a pharmaceutically acceptable salt thereof, wherein each of variables X^1, X^2, X^3, R^1, R^2, Ring A, m, Ring

T, L^x, X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

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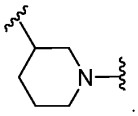
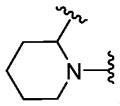
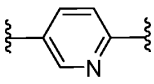
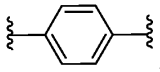
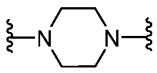
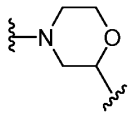
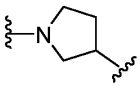
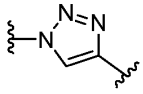
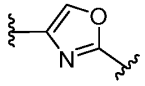
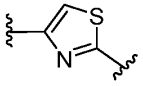
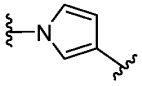
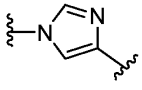
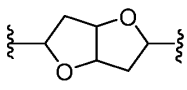
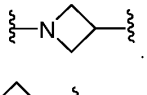
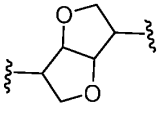
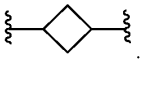
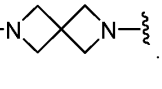
[00169] As defined above and described herein, L is a bivalent moiety that connects IRAK to LBM.

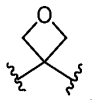
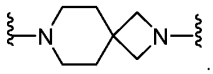
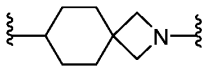
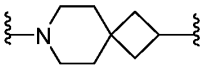
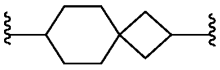
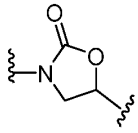
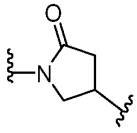
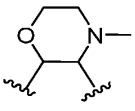
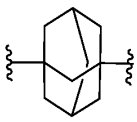
[00170] In some embodiments, L is a bivalent moiety that connects IRAK to LBM.

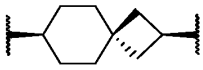
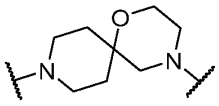
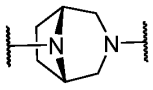
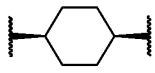
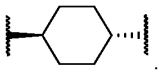
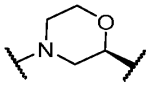
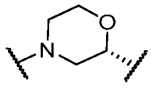
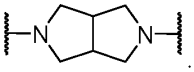
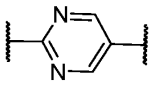
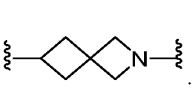
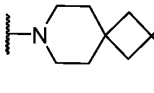
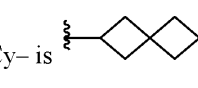
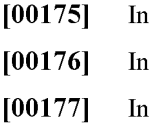
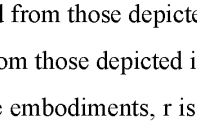
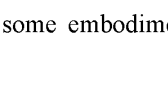
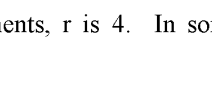
[00171] In some embodiments, L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -C(D)(H)-, -$C(D)_2$-, -CRF-, -CF_2-, -Cy-, -O-, -N(R)-, -$Si(R)_2$-, -Si(OH)(R)-, -$Si(OH)_2$-, -P(O)(OR)-, -P(O)(R)-, -$P(O)(NR_2)$-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -N(R)$S(O)_2$-, -$S(O)_2$N(R)-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)C(O)O-,  ,  ,  ,  ,  , or  , wherein: each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-12 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-12 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[00172] In some embodiments, each –Cy– is independently an optionally substituted bivalent phenylenyl. In some embodiments, each –Cy– is independently an optionally substituted 8-10 membered bicyclic arylenyl. In some embodiments, each –Cy– is independently an optionally substituted 4-7 membered saturated or partially unsaturated carbocyclylenyl. In some embodiments, each –Cy– is independently an optionally substituted 4-12 membered saturated or partially unsaturated spiro

carbocyclylenyl. In some embodiments, each –Cy– is independently an optionally substituted 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl. In some embodiments, each –Cy– is independently an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each –Cy– is independently an optionally substituted 4-12 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each –Cy– is independently an optionally substituted 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each –Cy– is independently an optionally substituted 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each –Cy– is independently an optionally substituted 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00173] In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some

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[00174] In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is . In some embodiments, –Cy– is  . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some embodiments, –Cy– is . In some embodiments, –Cy– is .

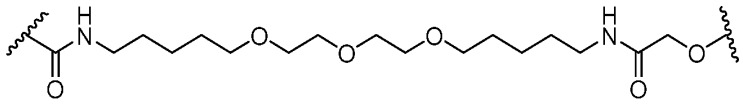
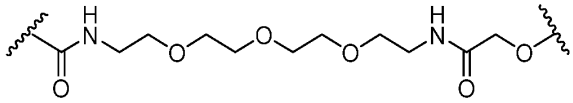
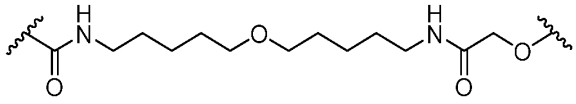
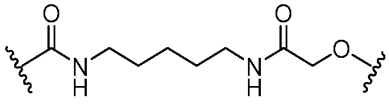
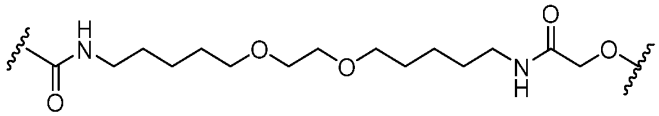
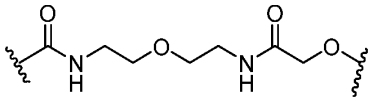
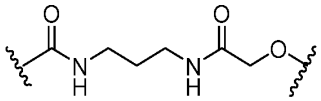
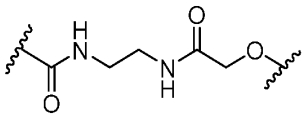
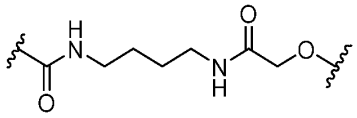
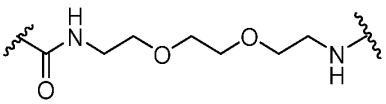
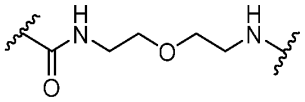
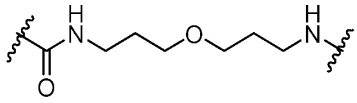
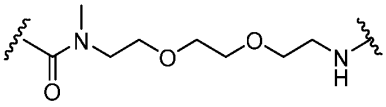
[00175] In some embodiments, -Cy- is selected from those depicted in **Table 1**, below.

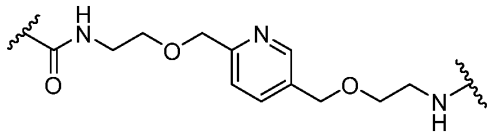
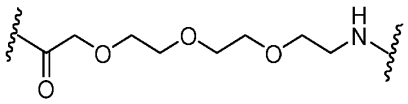
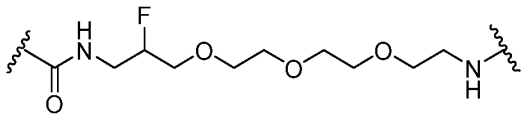
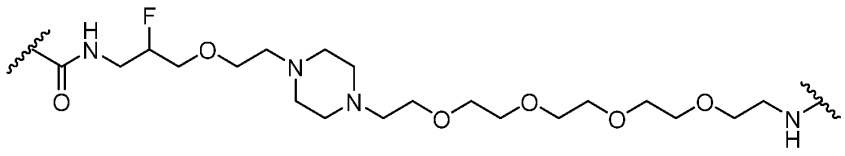
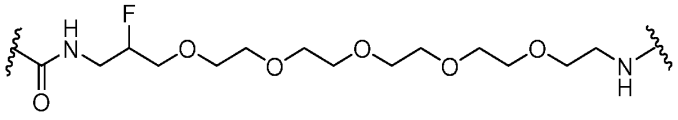
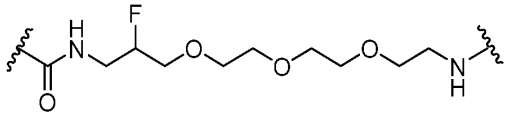
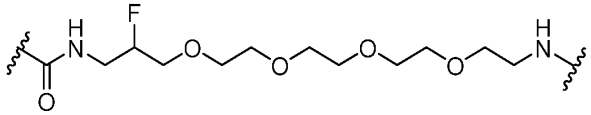
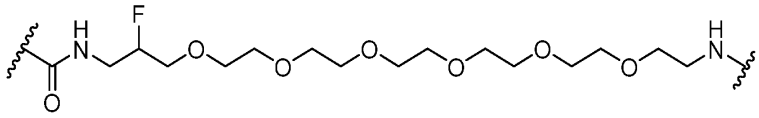
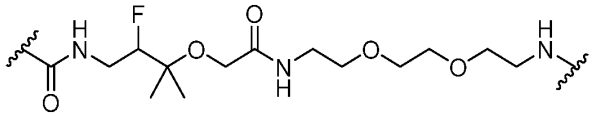
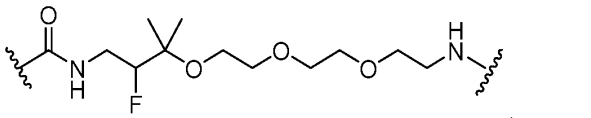
[00176] In some embodiments, L is selected from those depicted in **Table 1**, below.

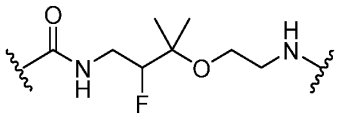
[00177] In some embodiments, r is 0. In some embodiments, r is 1. In some embodiments, r is 2. In some embodiments, r is 3. In some embodiments, r is 4. In some embodiments, r is 5. In some

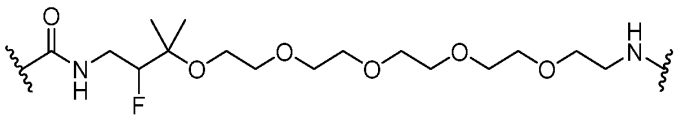
embodiments, r is 6. In some embodiments, r is 7. In some embodiments, r is 8. In some embodiments, r is 9. In some embodiments, r is 10.

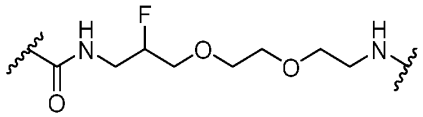
[00178] In some embodiments, r is selected from those depicted in **Table 1**, below.

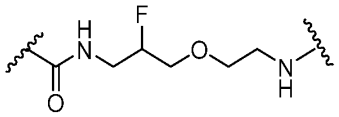
[00179] In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  .

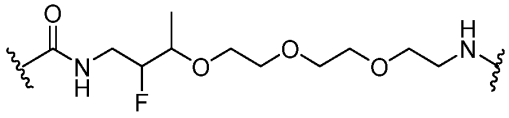
some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is

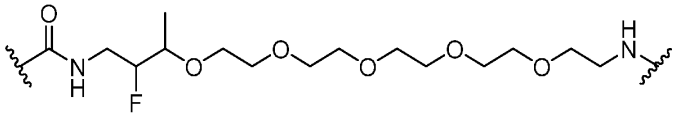

. In some embodiments, L is

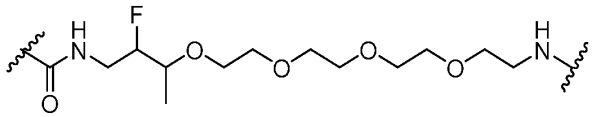

. In some embodiments, L is

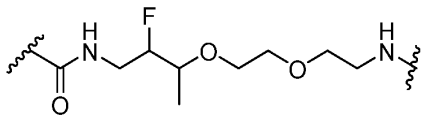

. In some embodiments, L is

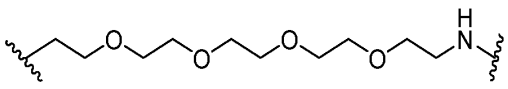

. In some embodiments, L is

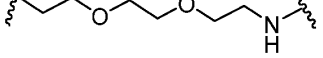

. In some embodiments, L is

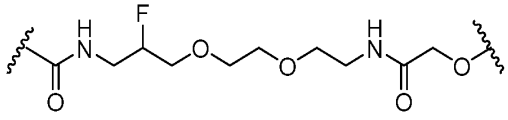

. In some embodiments, L is

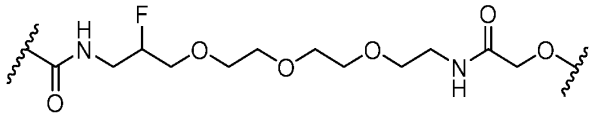

. In some embodiments, L is

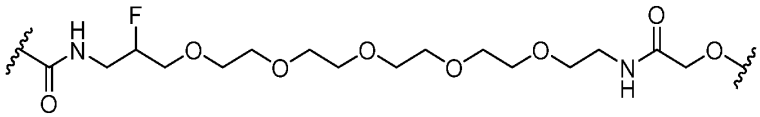

. In some embodiments, L is

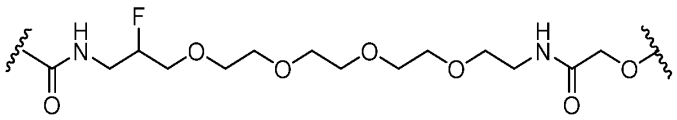

. In some embodiments, L is

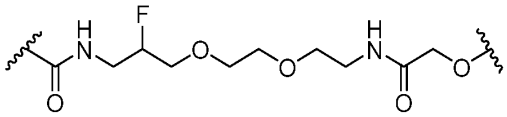

. In some embodiments, L is

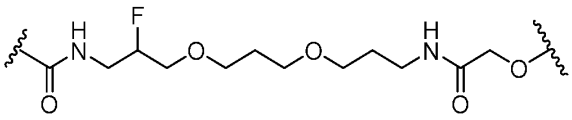

. In some embodiments, L is

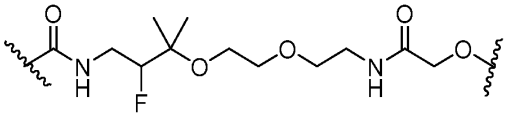

. In some embodiments, L is

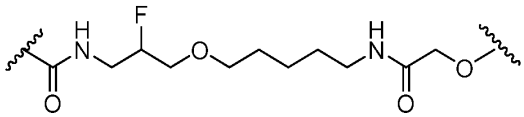

. In some embodiments, L is

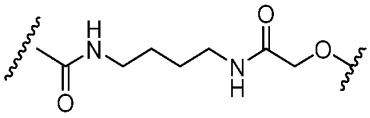

. In some embodiments, L is

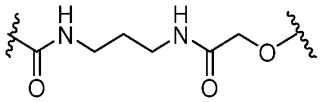

. In some embodiments, L is

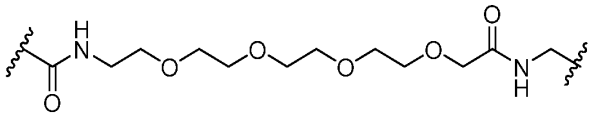

. In some embodiments, L is

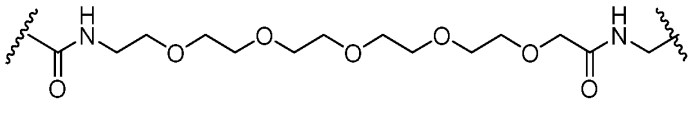

. In some embodiments, L is

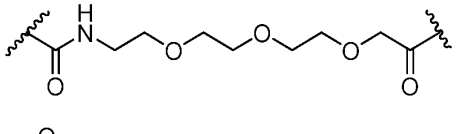

. In some embodiments, L is

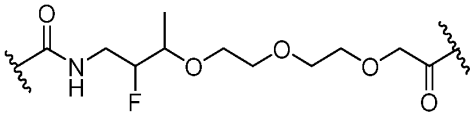

. In some embodiments, L is

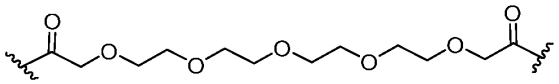

. In some embodiments, L is

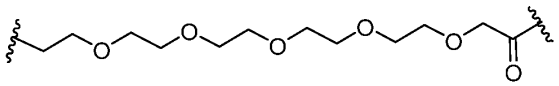

. In some embodiments, L is

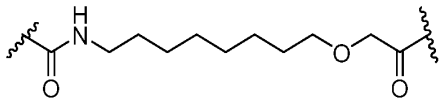

. In some embodiments, L is

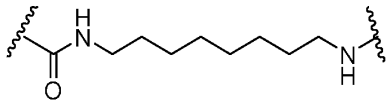

. In some embodiments, L is

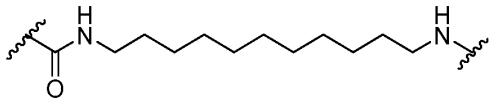

. In some embodiments, L is

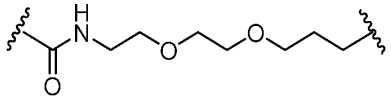

. In some embodiments, L is

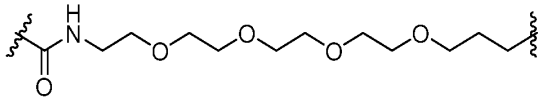

. In some embodiments, L is

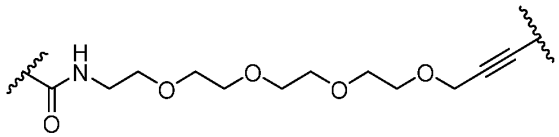

. In some embodiments, L is

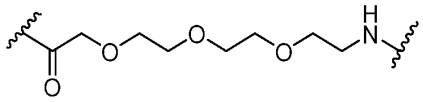

. In some embodiments, L is

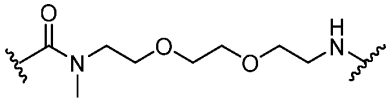

. In some embodiments, L is

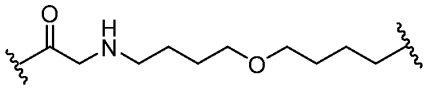

. In some embodiments, L is

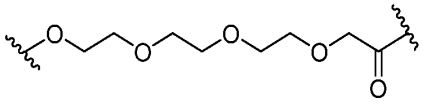

. In some embodiments, L is

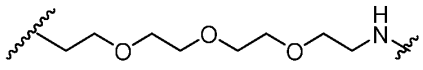
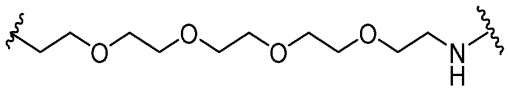
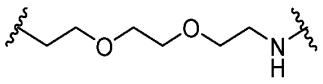
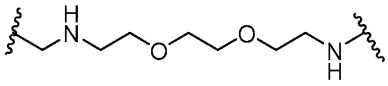
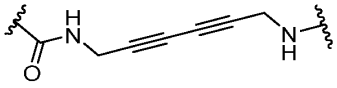
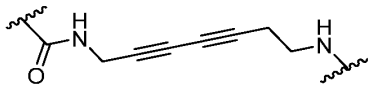
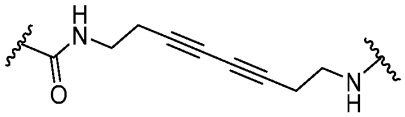
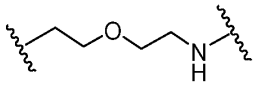
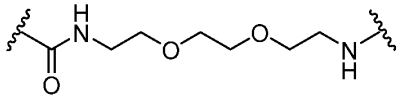
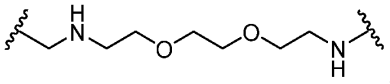
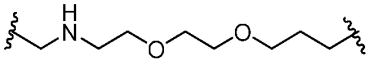
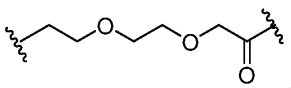
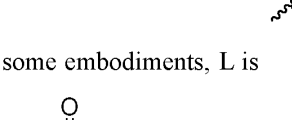
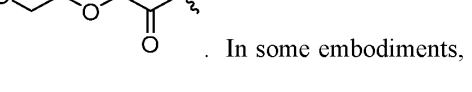
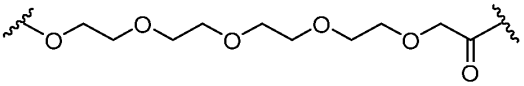
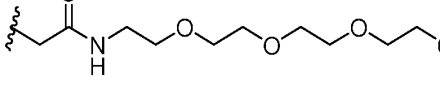
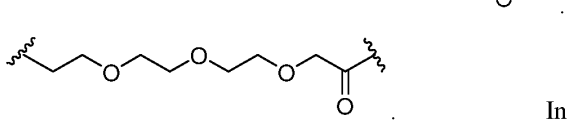
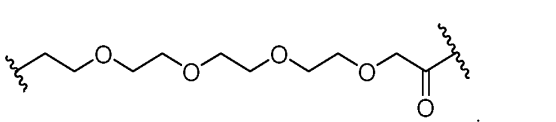

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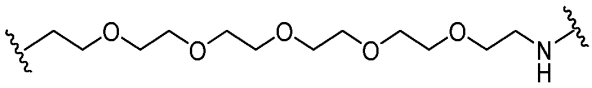
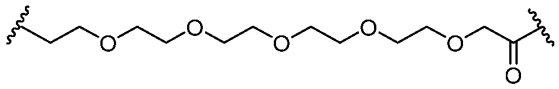
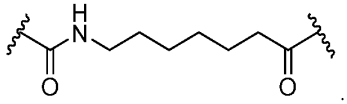
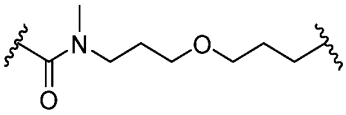
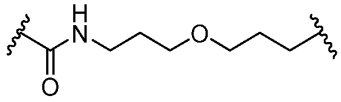
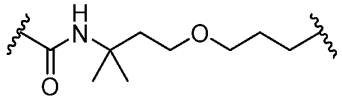
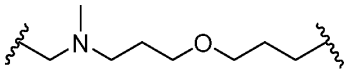
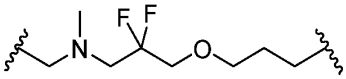
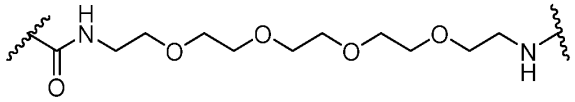
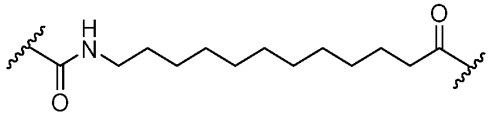
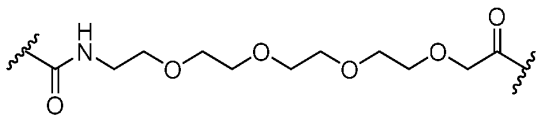
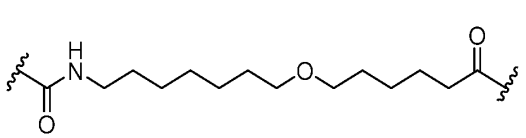
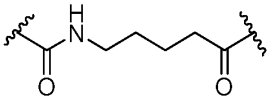
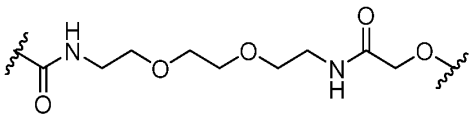
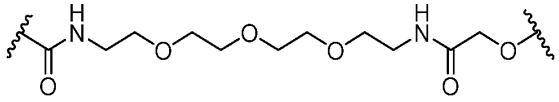

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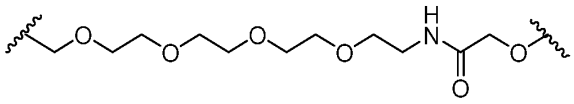

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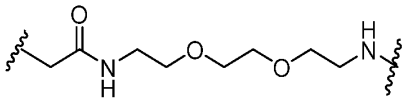

. In some embodiments, L is

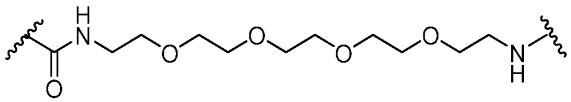

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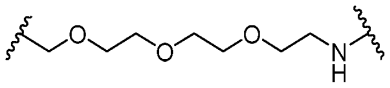
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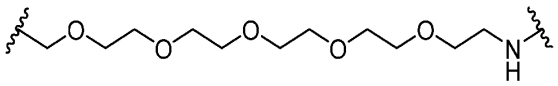
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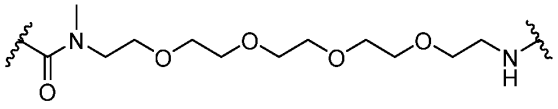

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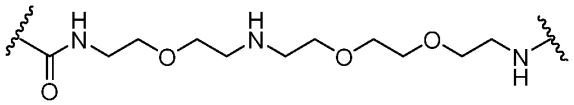

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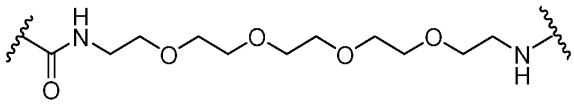

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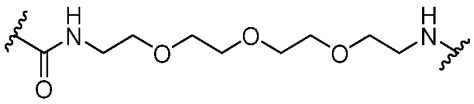

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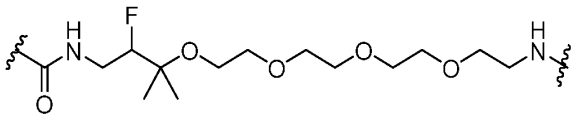

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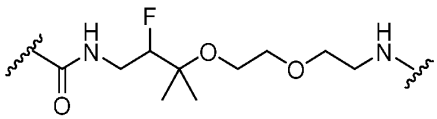

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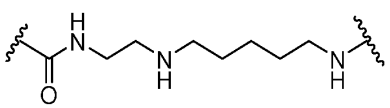

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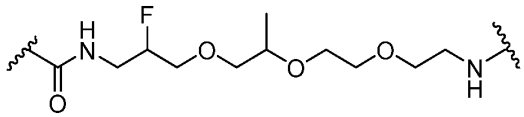

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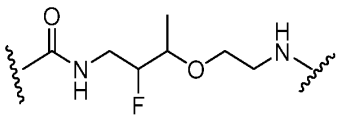

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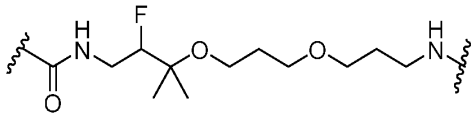

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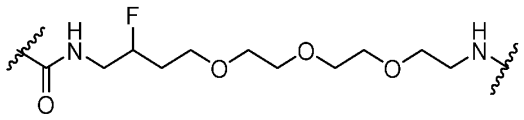

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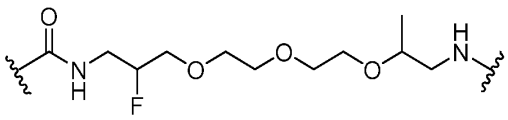

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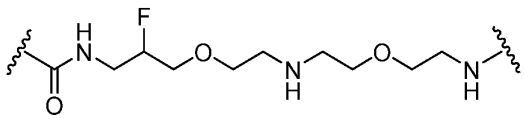

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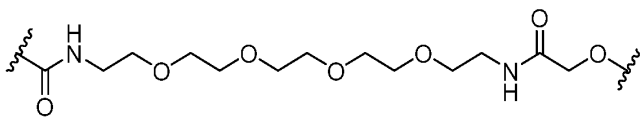

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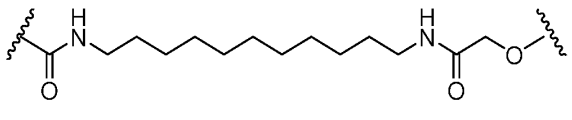

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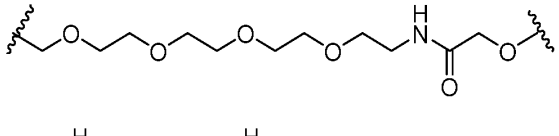

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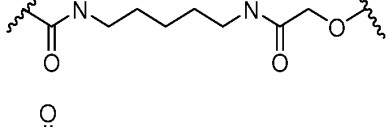

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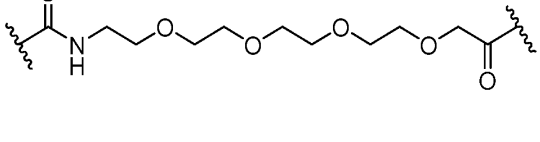

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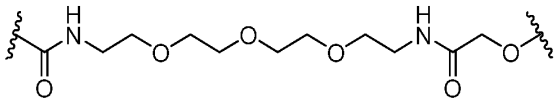

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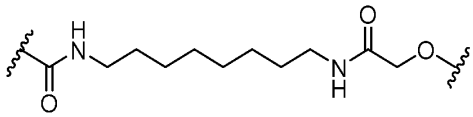

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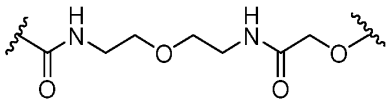

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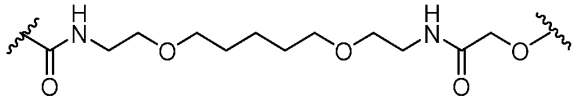

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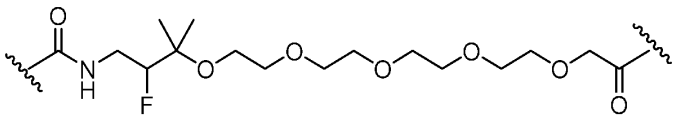

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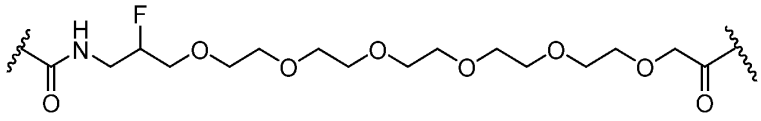

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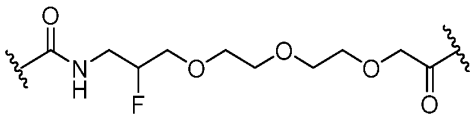

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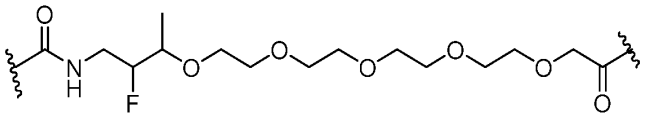

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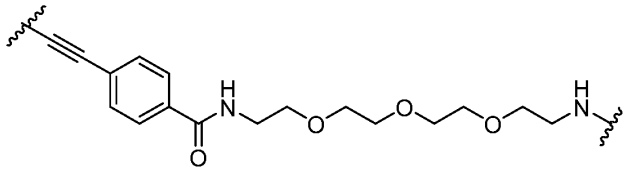

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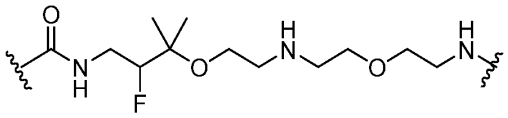

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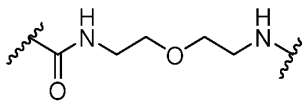

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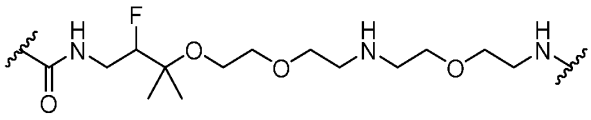

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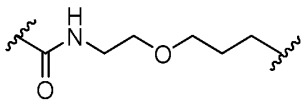

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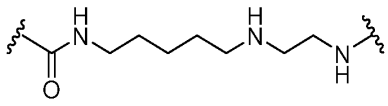

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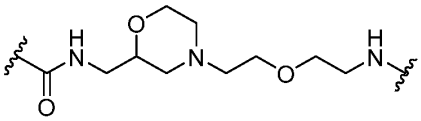
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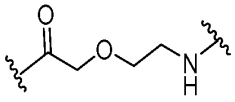
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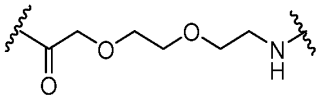
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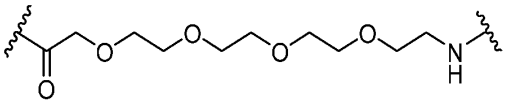
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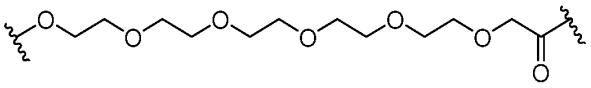
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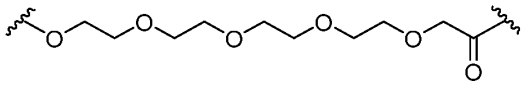
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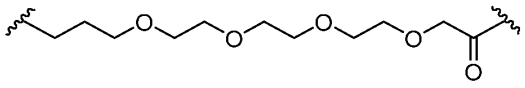
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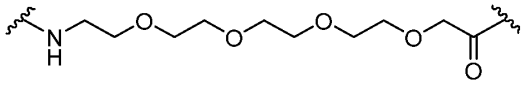
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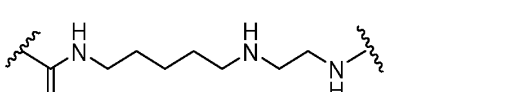
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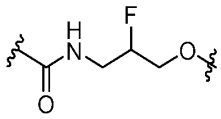


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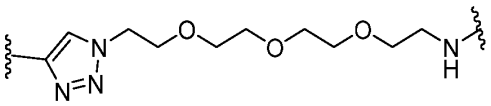


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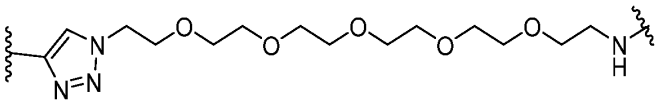
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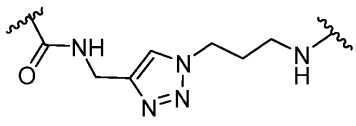
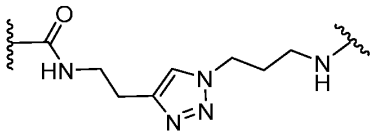
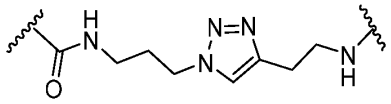
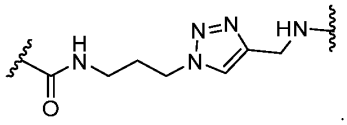
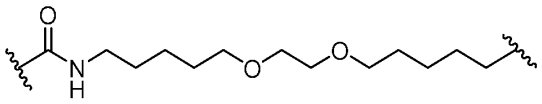
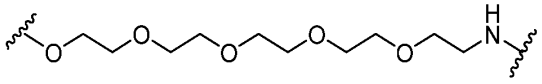
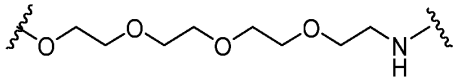
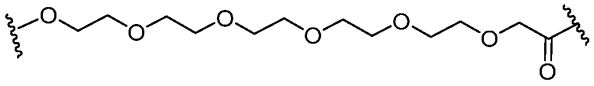
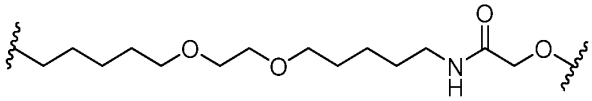
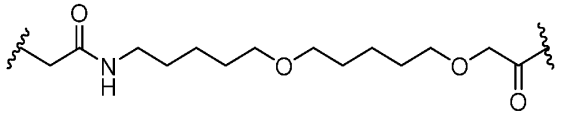
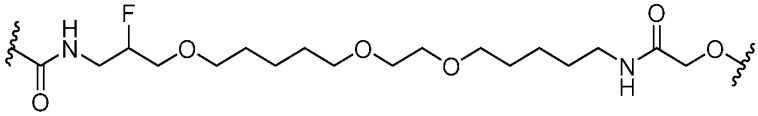
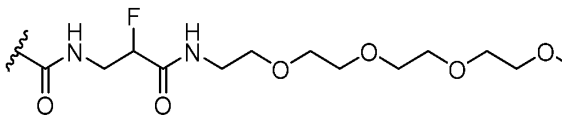
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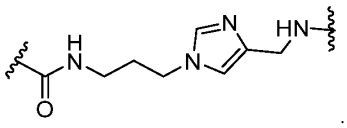
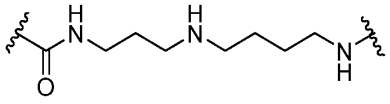
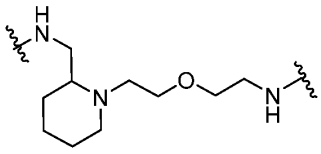
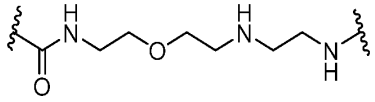
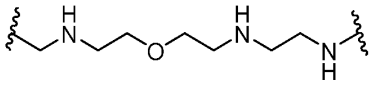
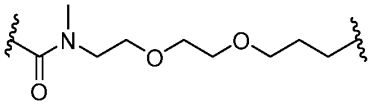
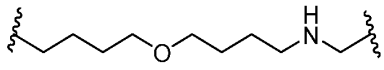
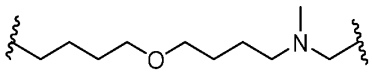
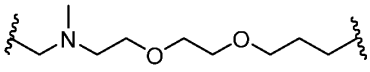
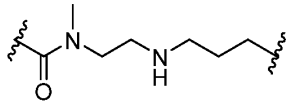
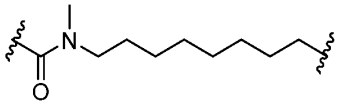
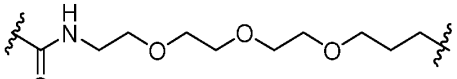
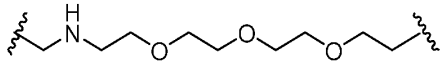
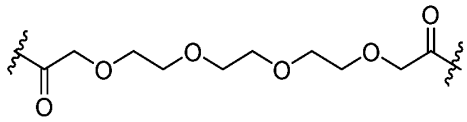
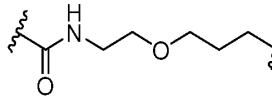
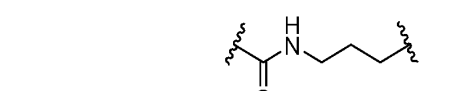
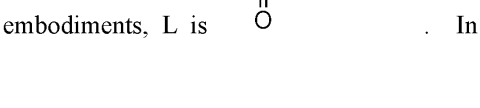
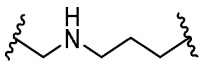


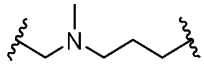
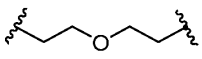
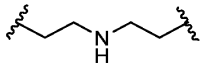
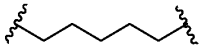
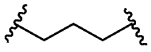
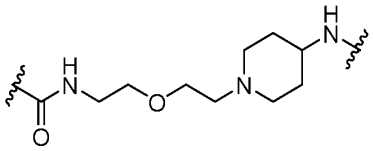
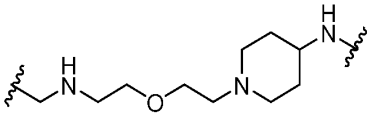
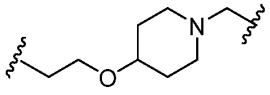
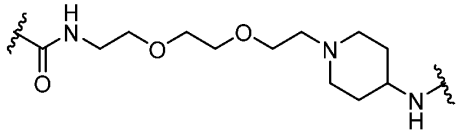
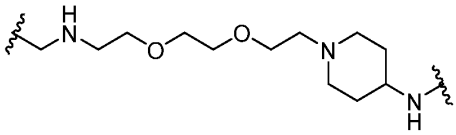
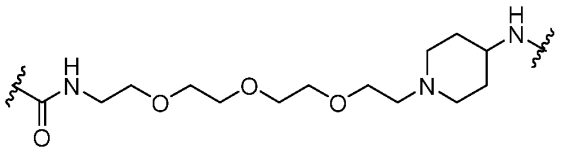
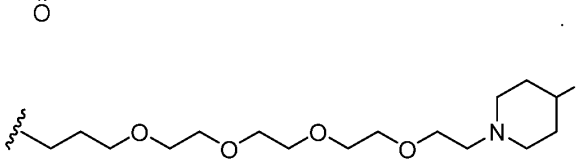
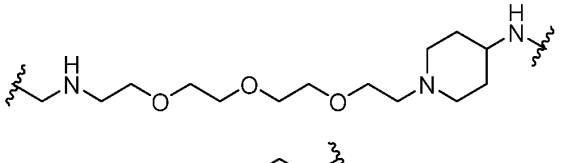
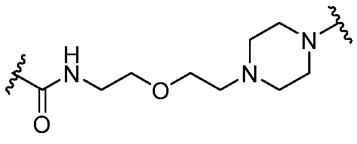
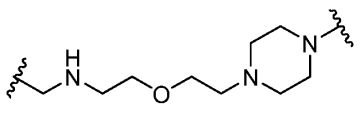
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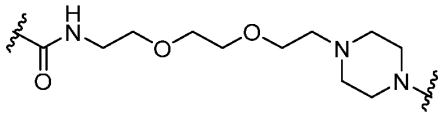
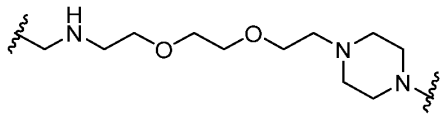
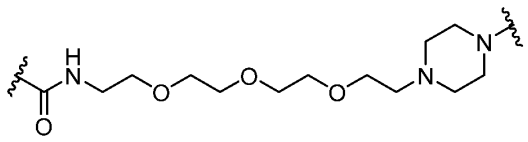
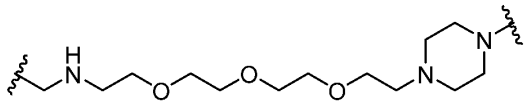
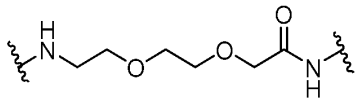
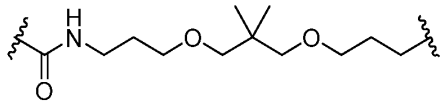
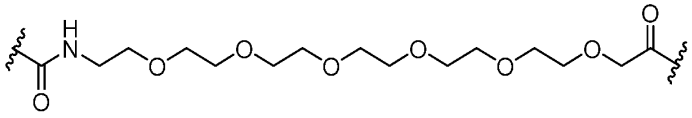
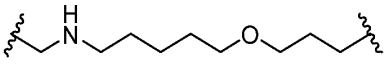
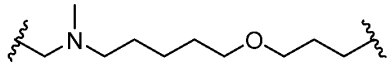
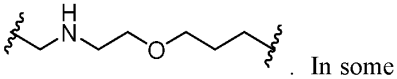
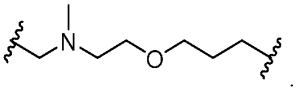
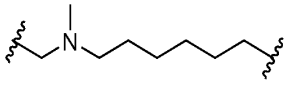
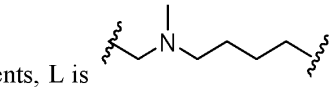
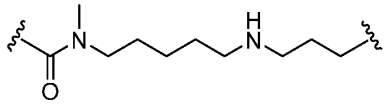
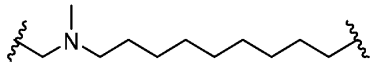
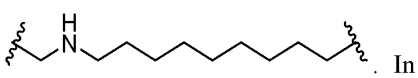
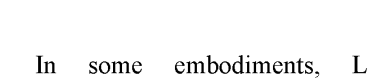


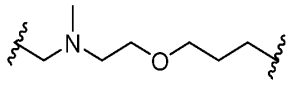
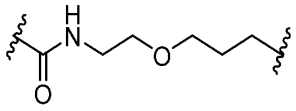
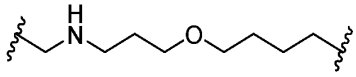
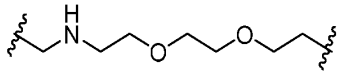
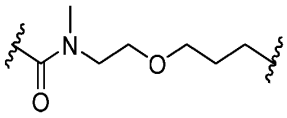
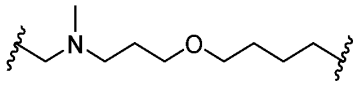
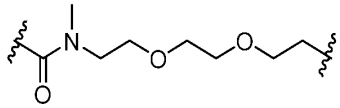
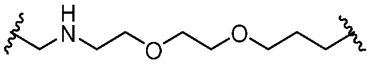
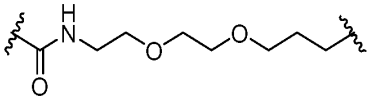
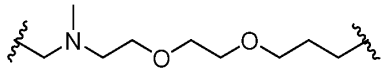
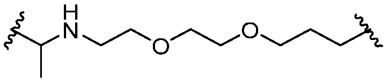
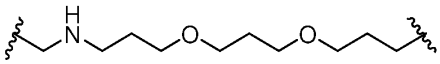
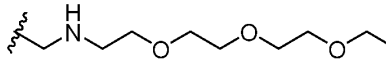
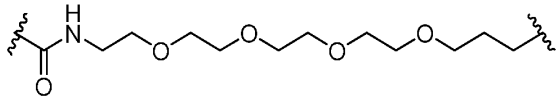
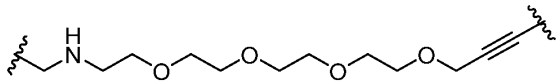
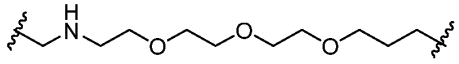
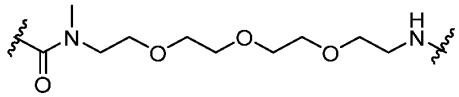
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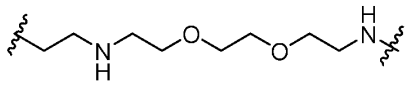
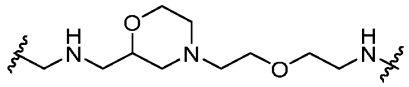
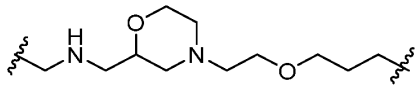
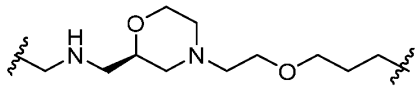
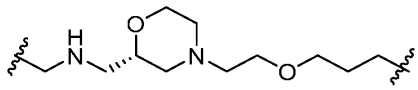
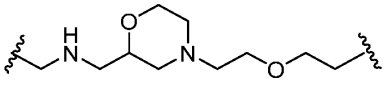
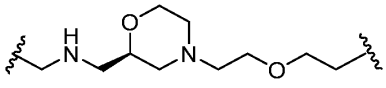
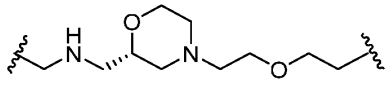
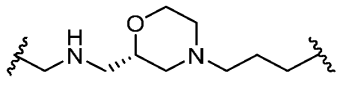
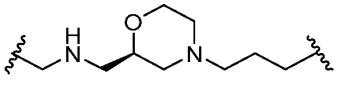
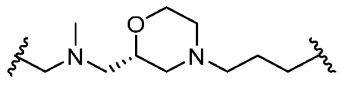
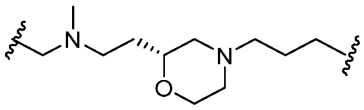
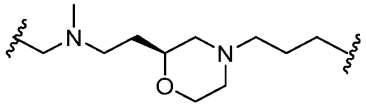
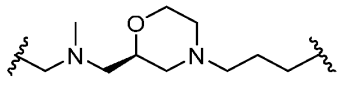
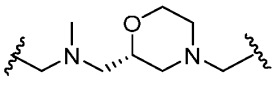
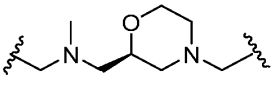
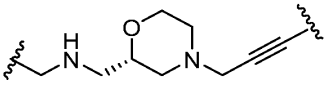

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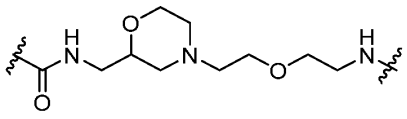
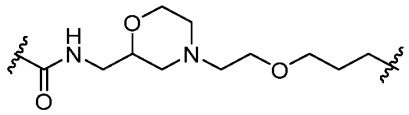
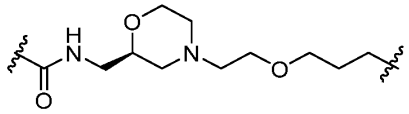
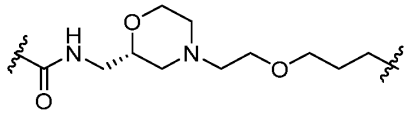
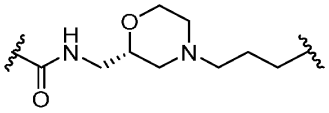
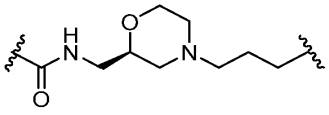
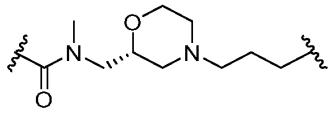
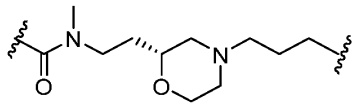
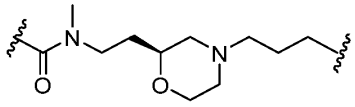
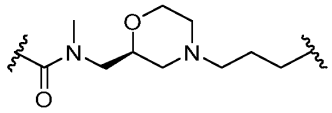
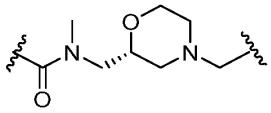
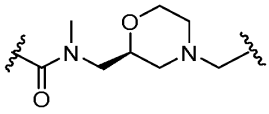
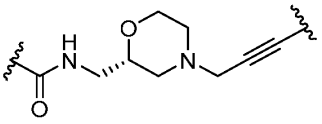
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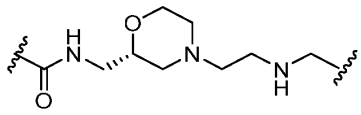
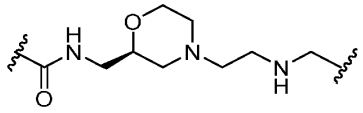
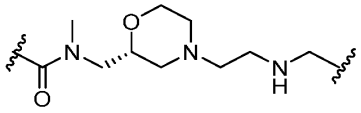
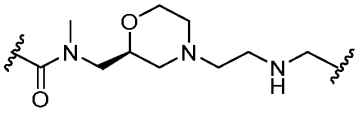
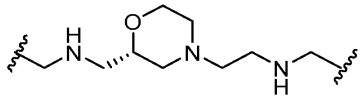
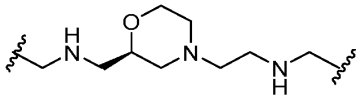
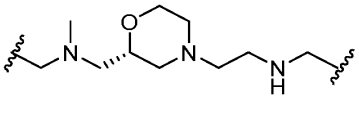
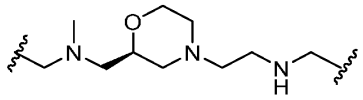
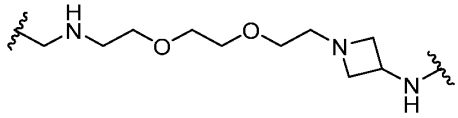
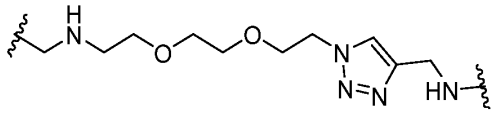
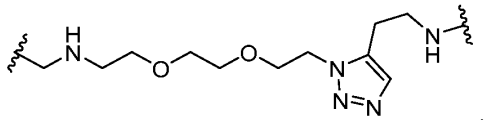
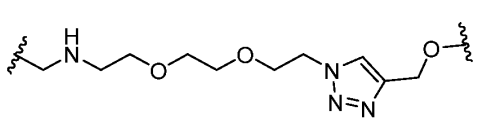
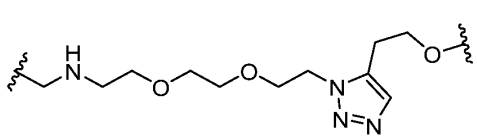
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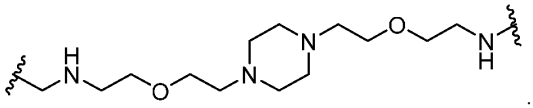
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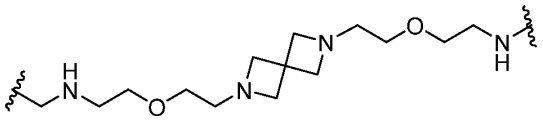
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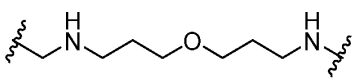
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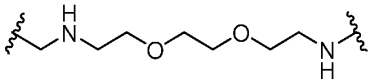
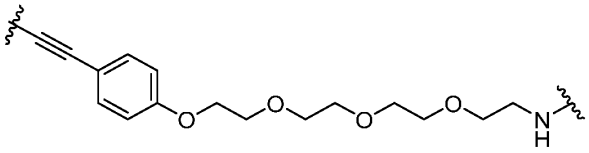
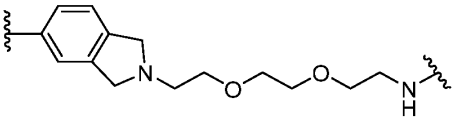


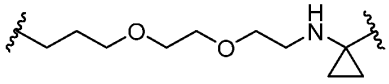
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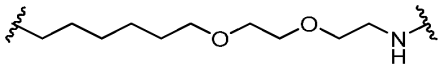
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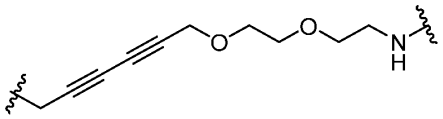
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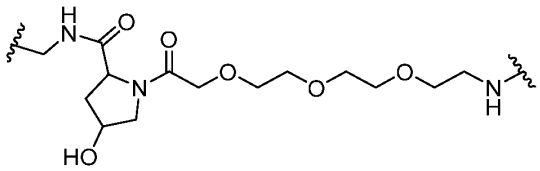
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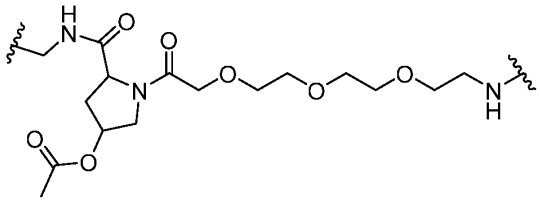
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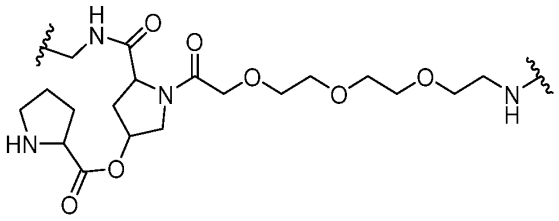
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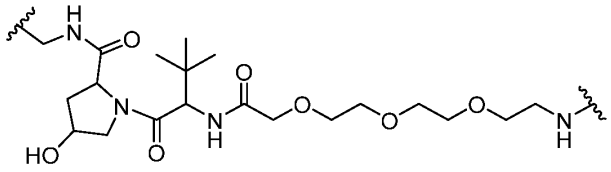
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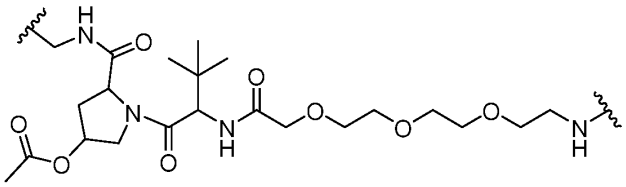
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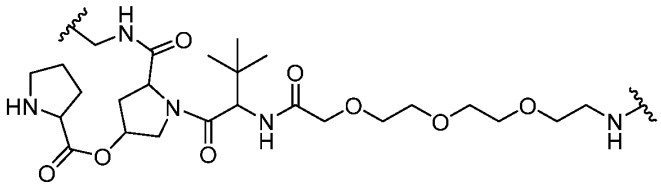
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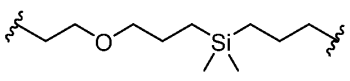
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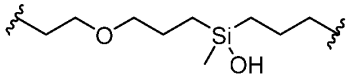
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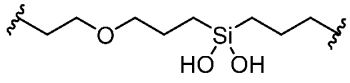
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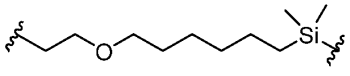
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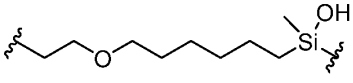
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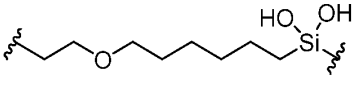
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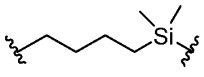
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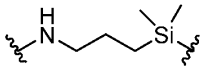
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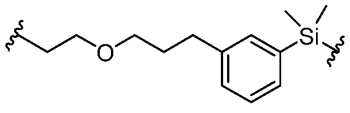
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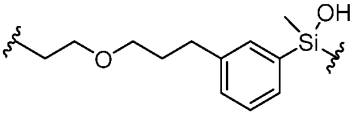
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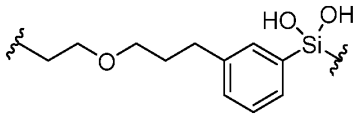
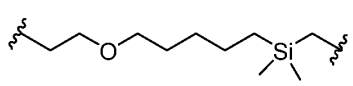
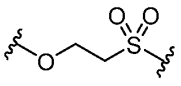
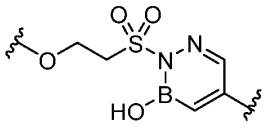
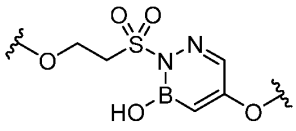
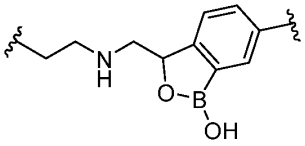
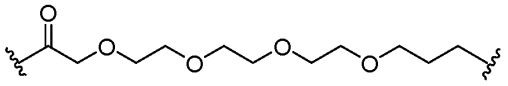
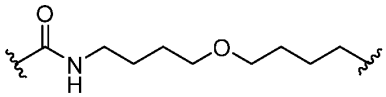
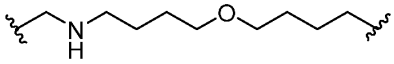
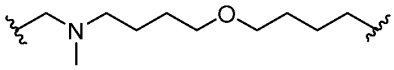
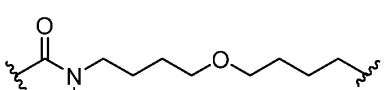
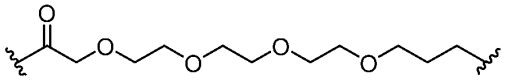
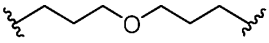
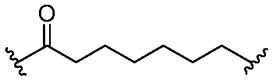
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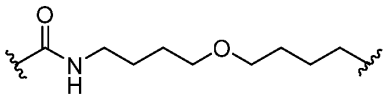
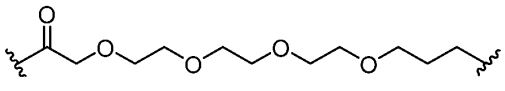
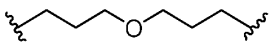
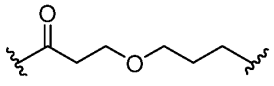
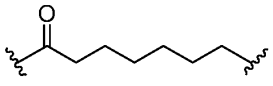
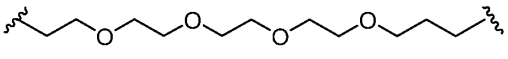
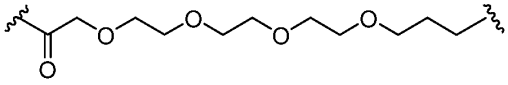
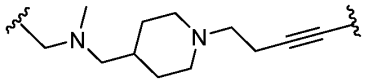
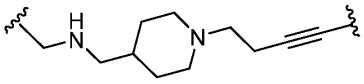
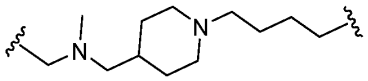
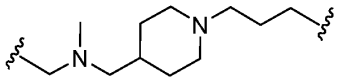
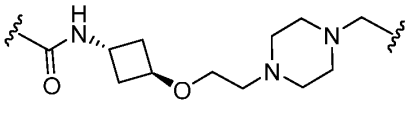
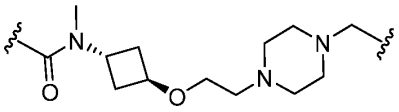
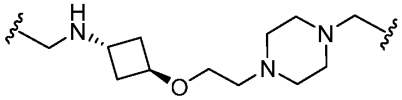
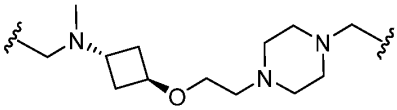
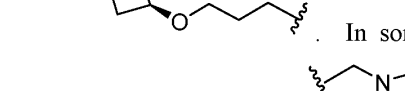
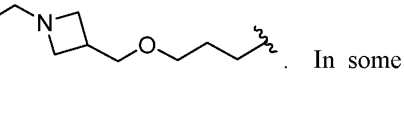


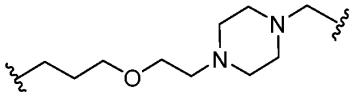
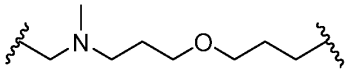
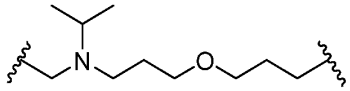
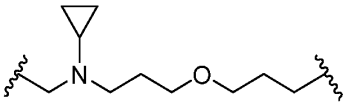
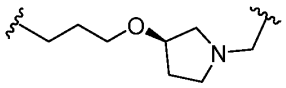
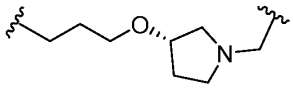
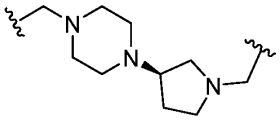
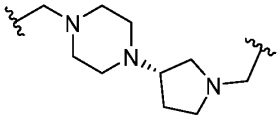
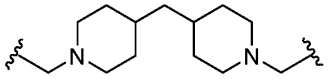
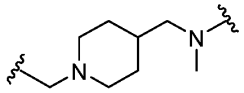
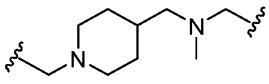
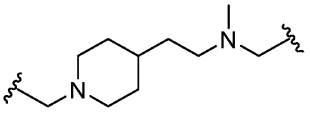
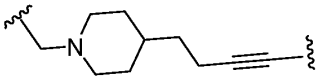
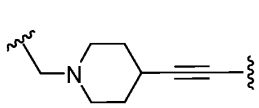
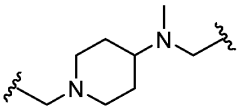
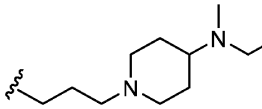
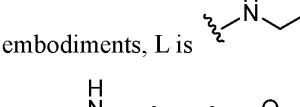
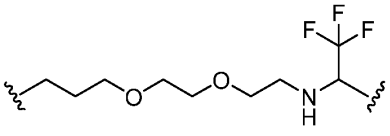
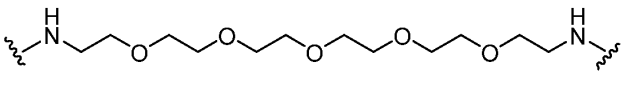
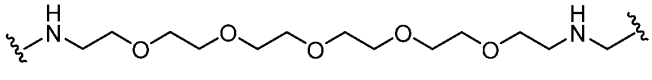
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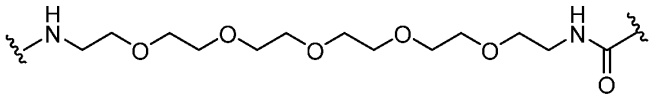
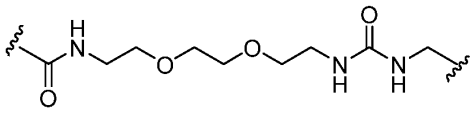
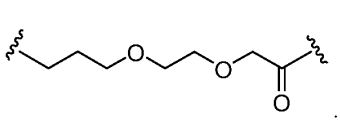
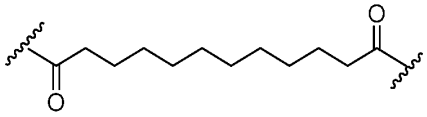
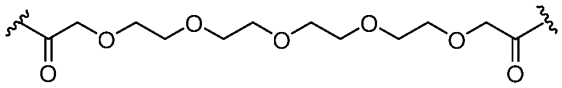
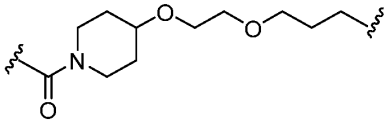
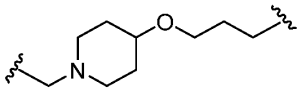
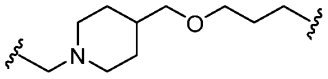
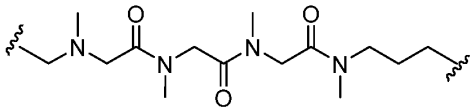
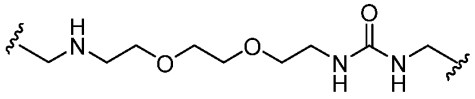
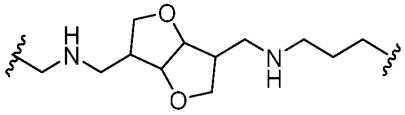
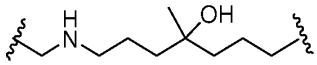
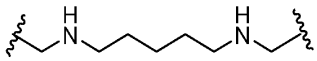
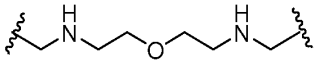
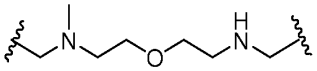
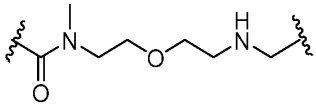


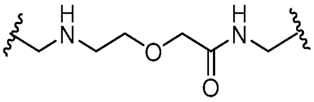
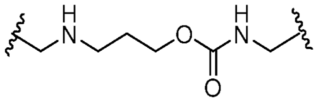
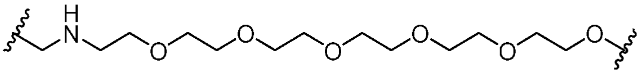
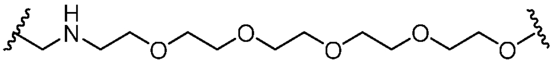
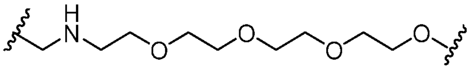
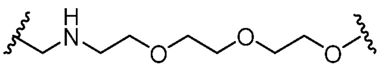
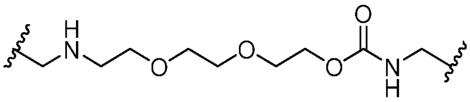
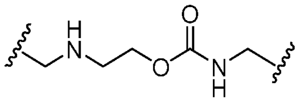
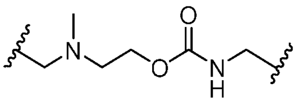
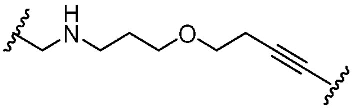
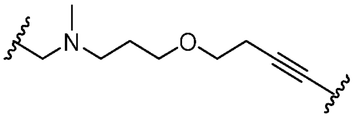
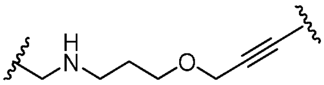
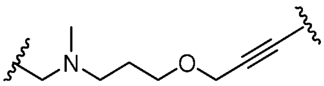
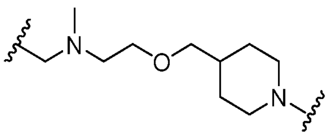
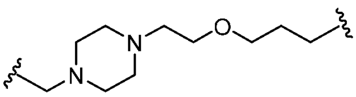
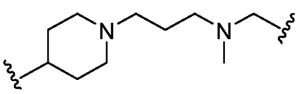
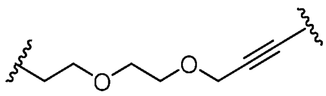
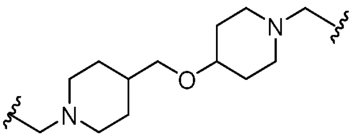
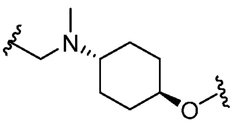
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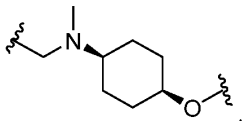
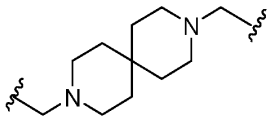
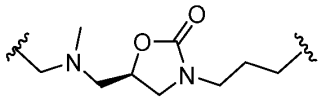
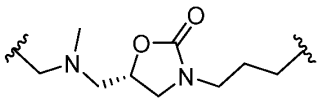
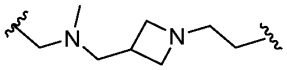
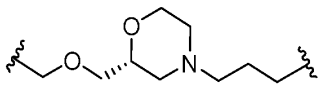
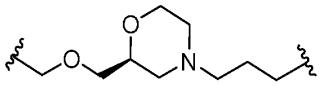
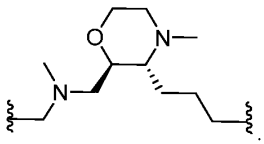
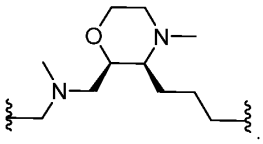
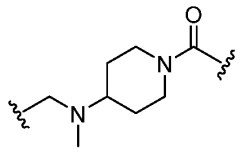
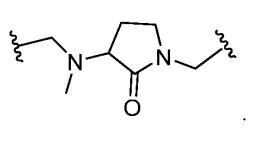
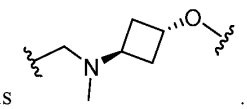
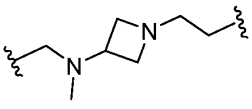
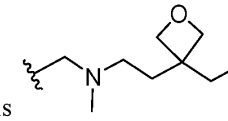
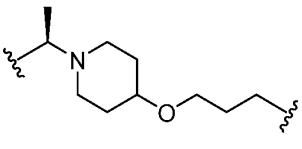
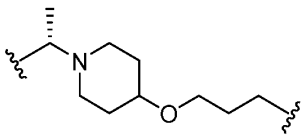
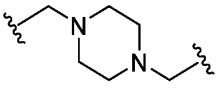
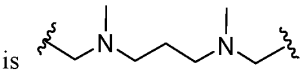
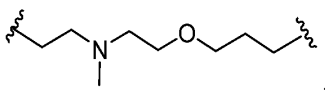
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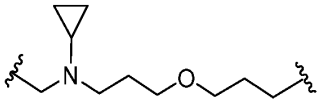
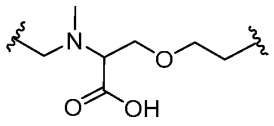
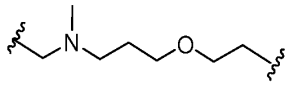
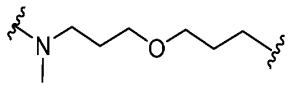
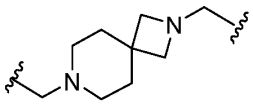
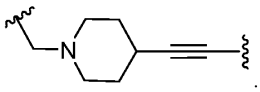
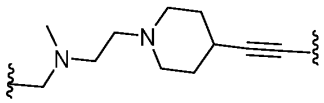
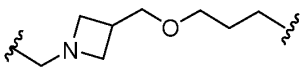
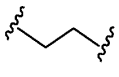
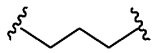
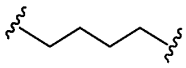
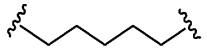
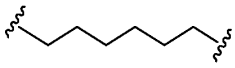
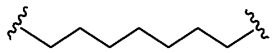
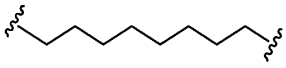
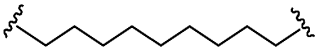
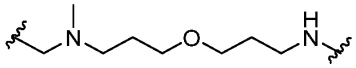
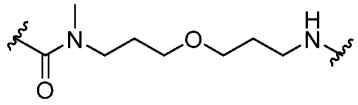
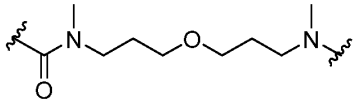
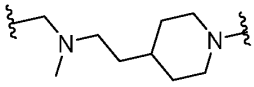
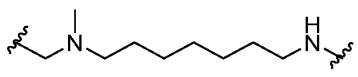
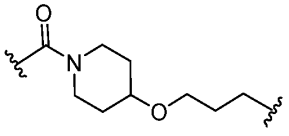
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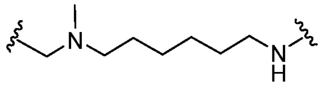
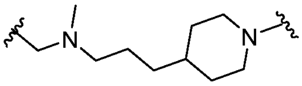
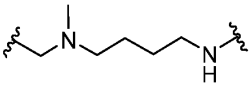
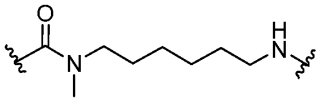
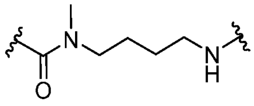
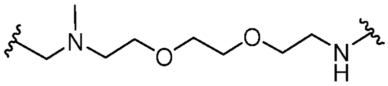
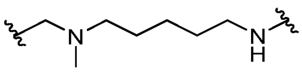
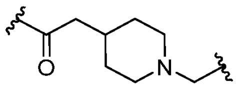
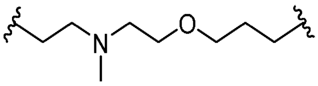
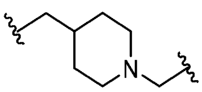
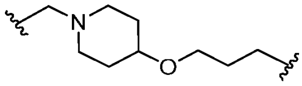
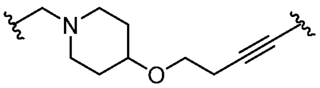
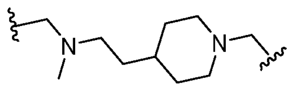
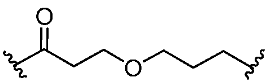
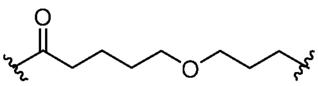
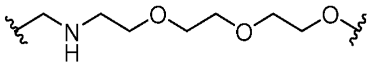
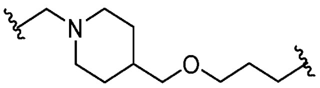
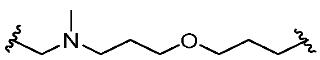
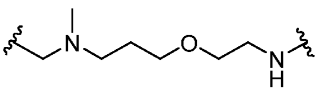
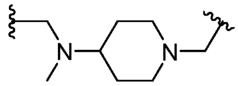
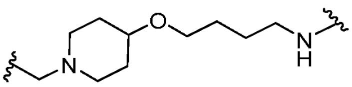
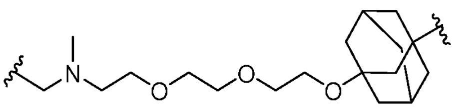
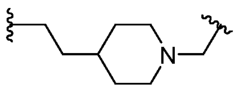
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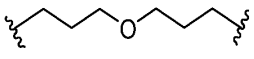
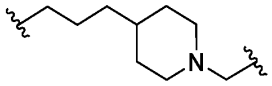
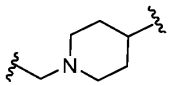
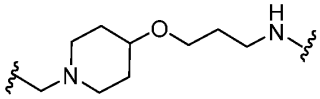
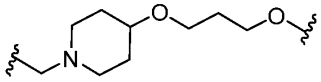
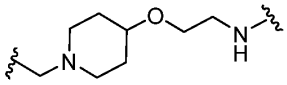
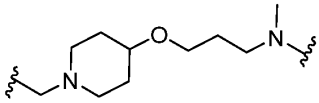
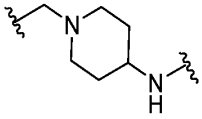
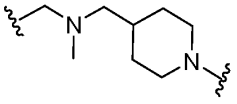
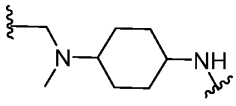
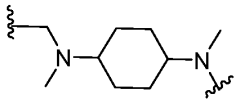
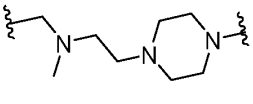
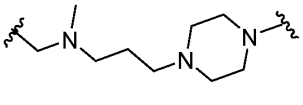
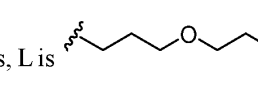
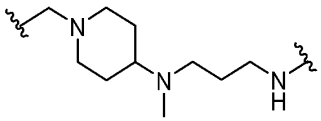
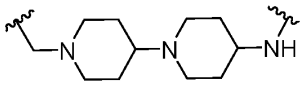
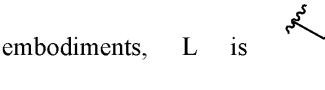
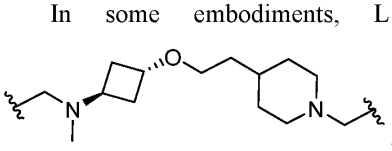
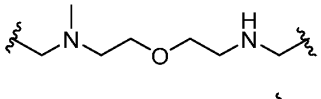
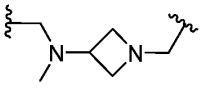
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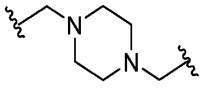
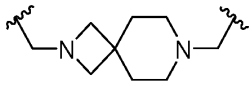
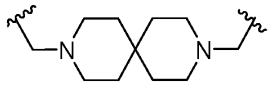
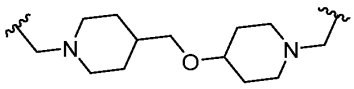
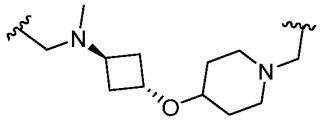
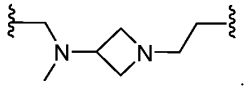
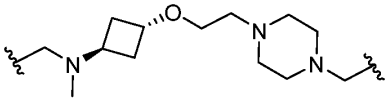
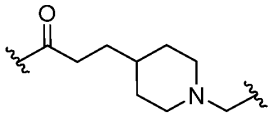
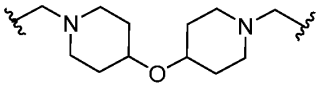
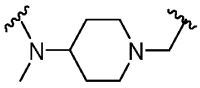
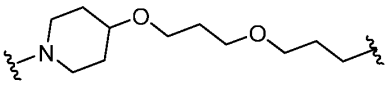
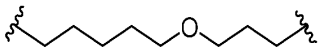
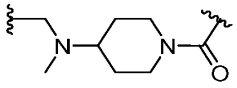
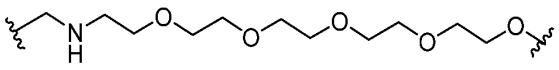
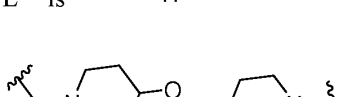
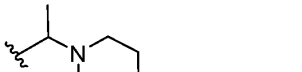
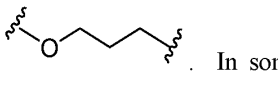
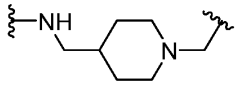
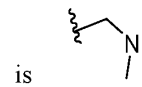
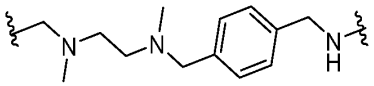
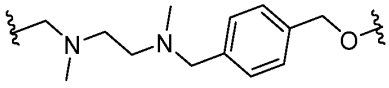
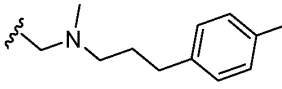
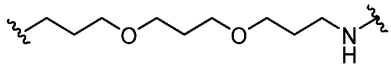
 . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is 

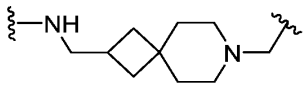
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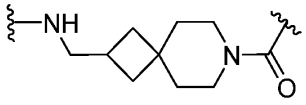
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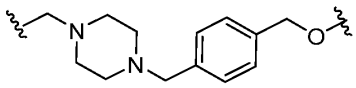
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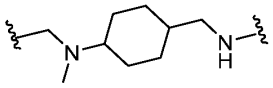
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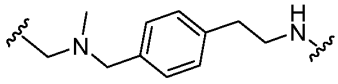
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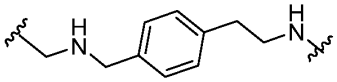


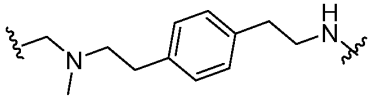
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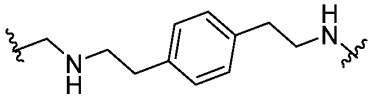
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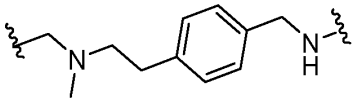
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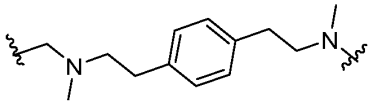
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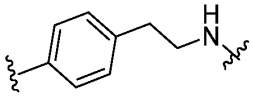
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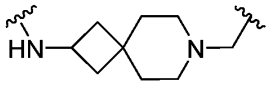
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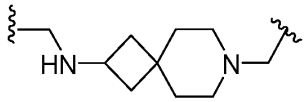
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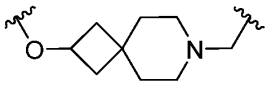
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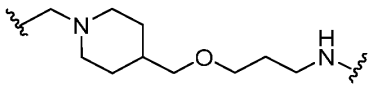
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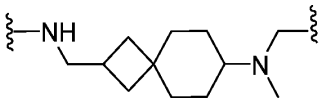
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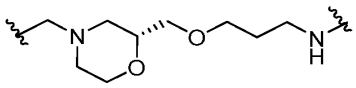
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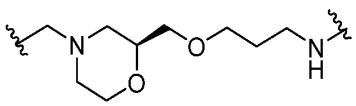
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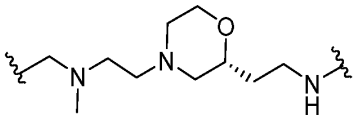
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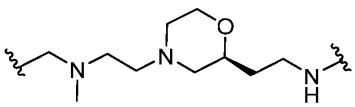
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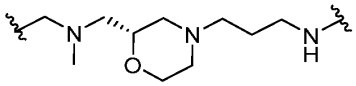
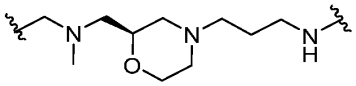
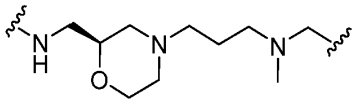
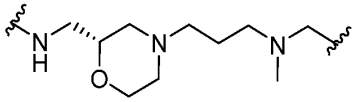
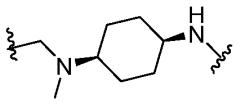
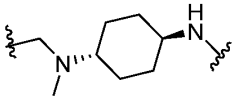
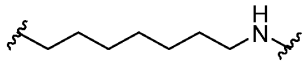
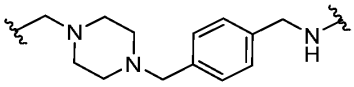
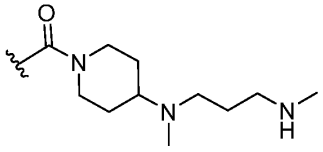
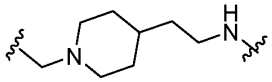
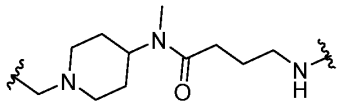
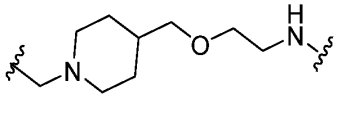
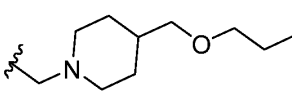
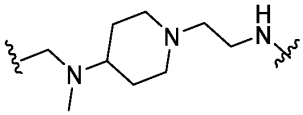
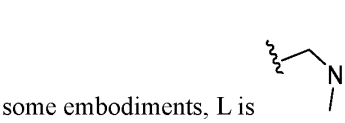
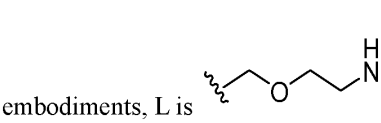
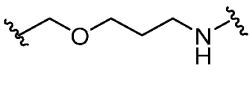
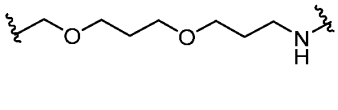
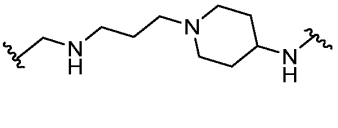
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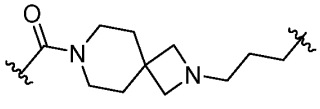
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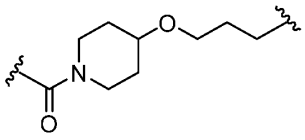
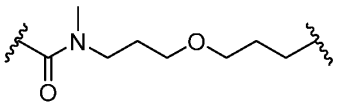
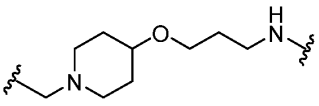
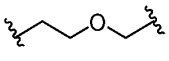
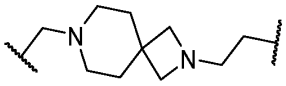
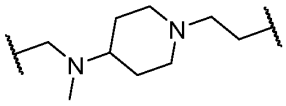
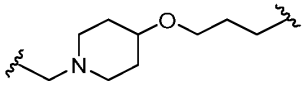
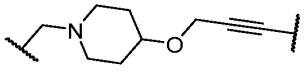
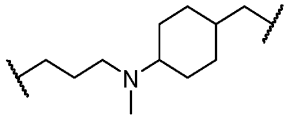
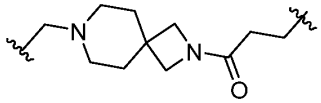
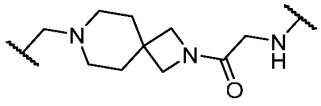
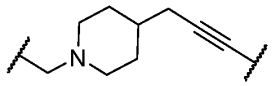
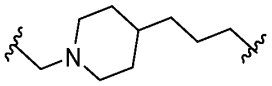
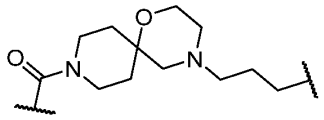
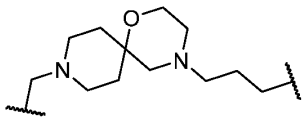
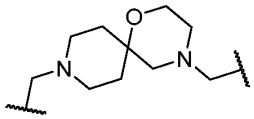
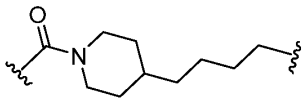
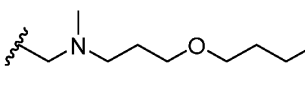
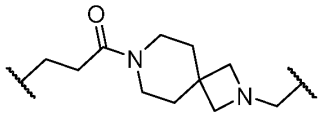
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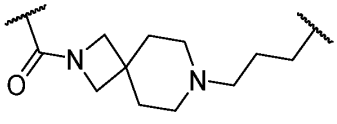
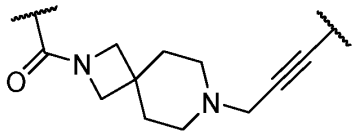
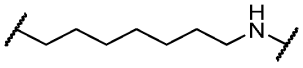
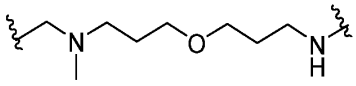
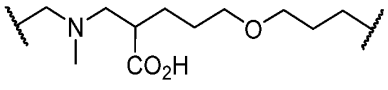
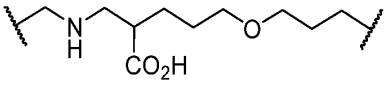
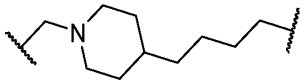
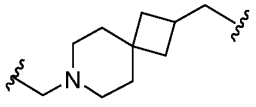
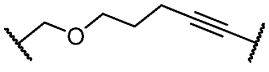
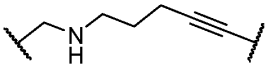
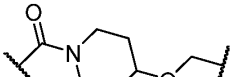
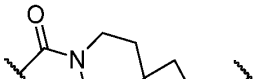
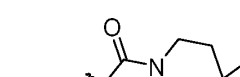
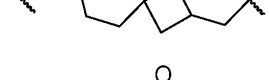
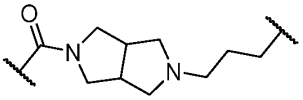
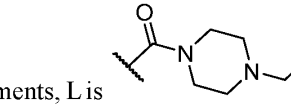
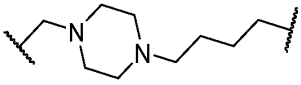
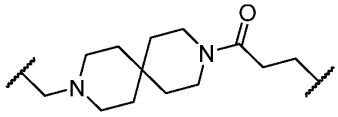
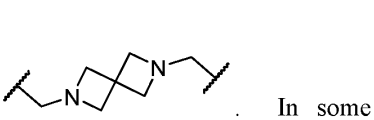
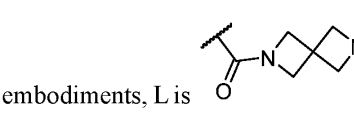
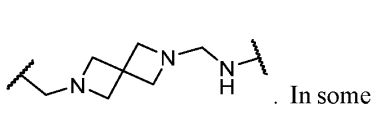
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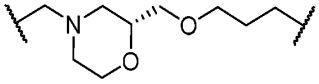
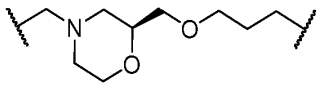
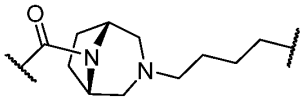
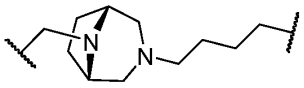
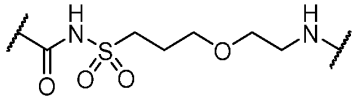
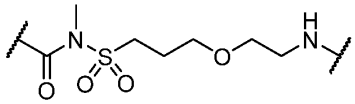
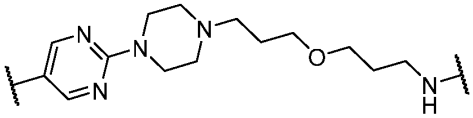
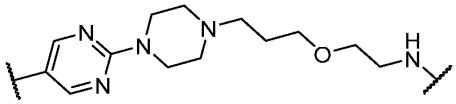
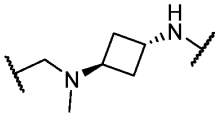
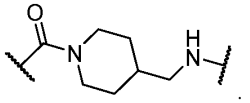
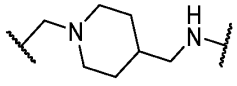
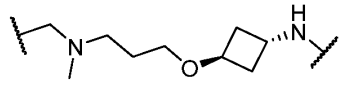
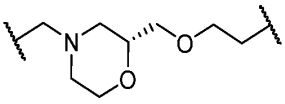
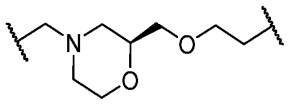
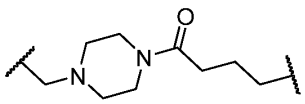
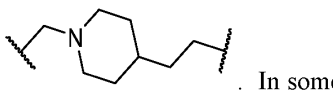
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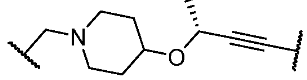
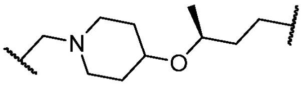
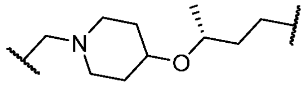
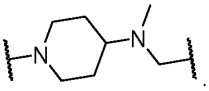
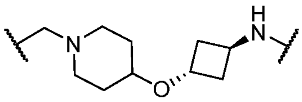
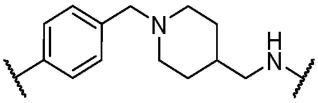
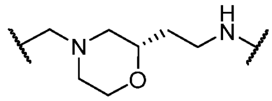
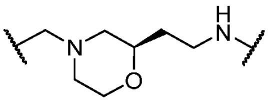
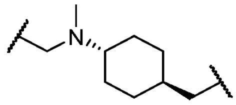
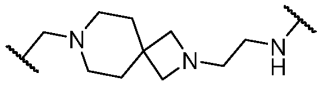
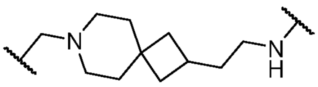
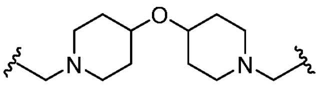
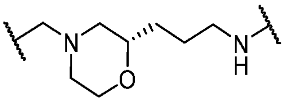
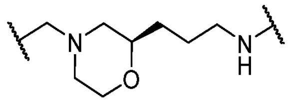
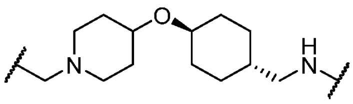
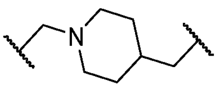
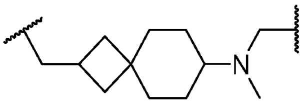
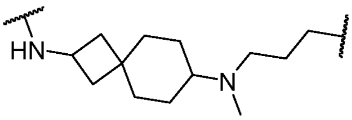
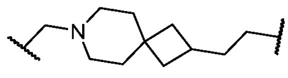
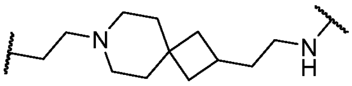
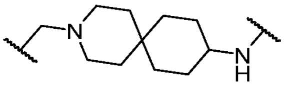
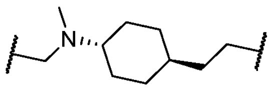
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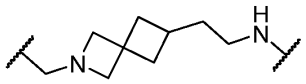
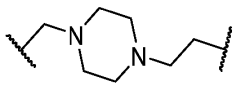
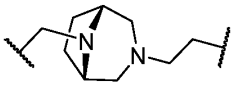
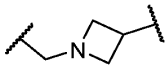
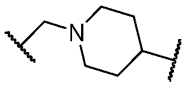
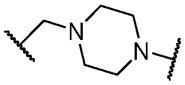
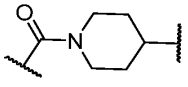
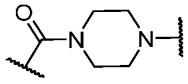
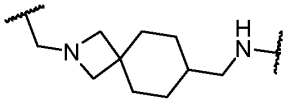
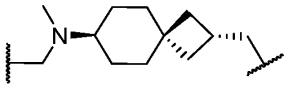
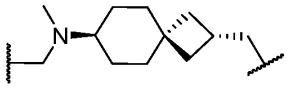
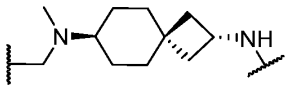
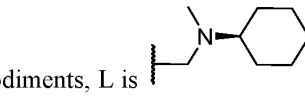
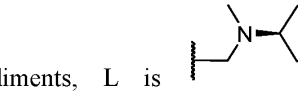
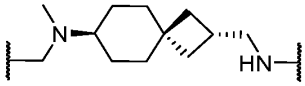
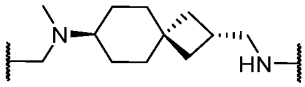
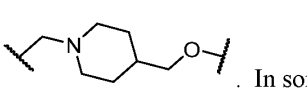
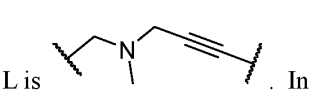
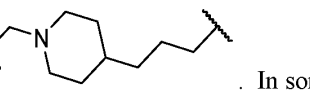
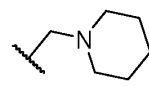
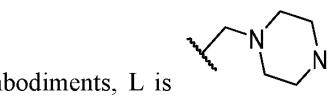
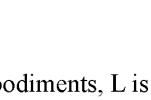
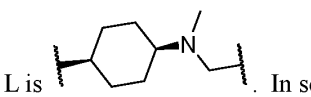
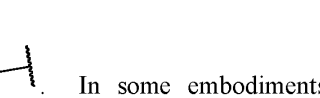
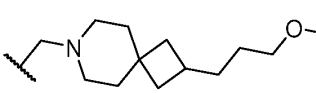
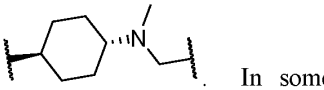
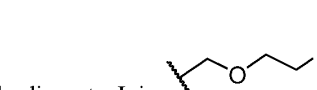
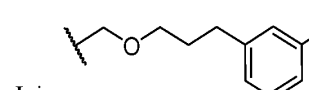
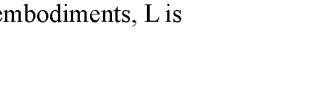
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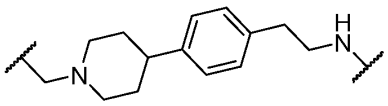
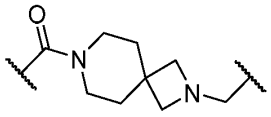
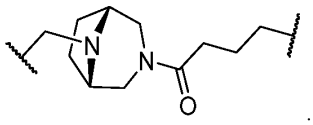
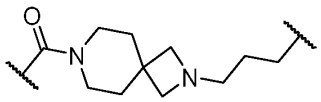
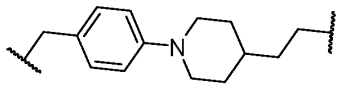
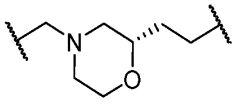
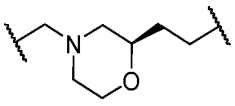
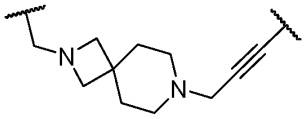
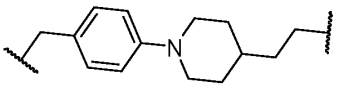
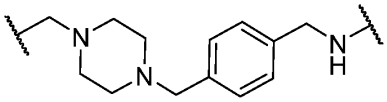
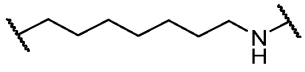
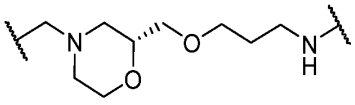
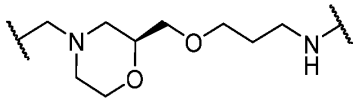
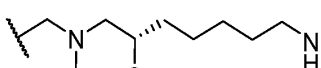
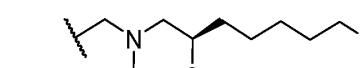
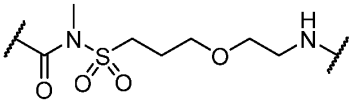
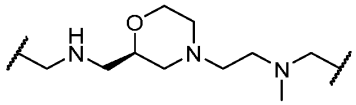
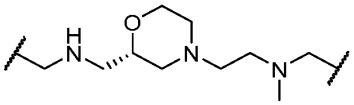

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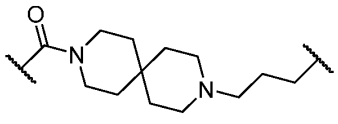
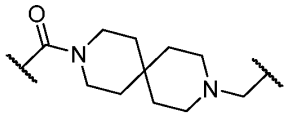
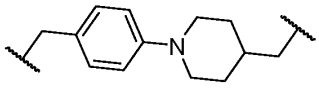
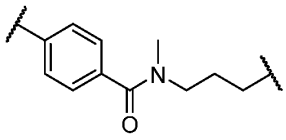
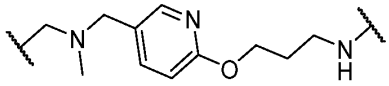
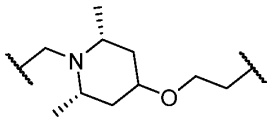
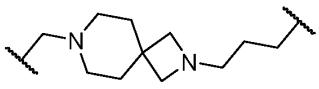
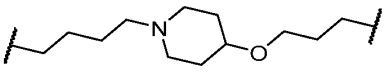
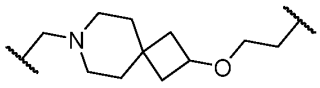
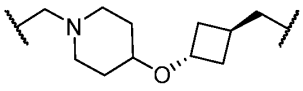
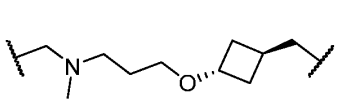
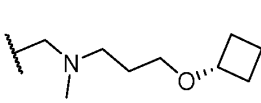
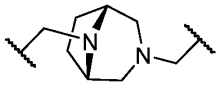
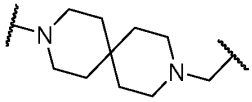
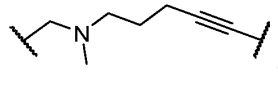
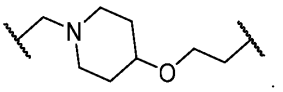
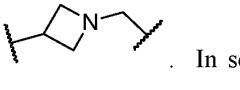
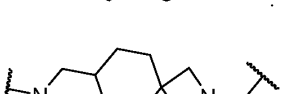
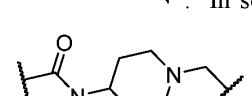
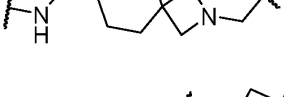
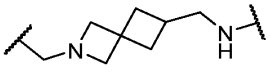
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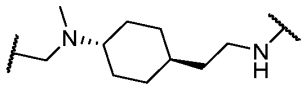
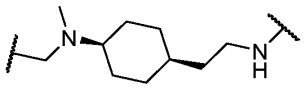
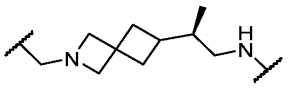
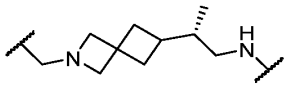
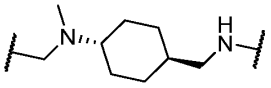
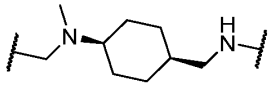
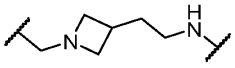
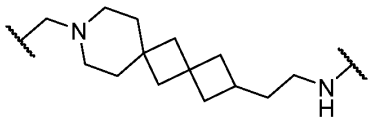
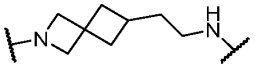
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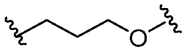
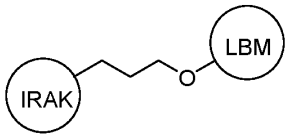
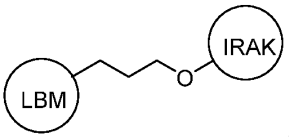
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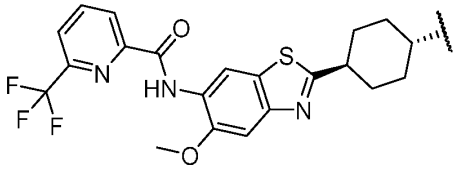
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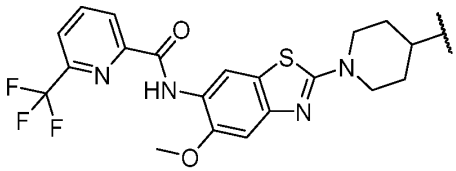
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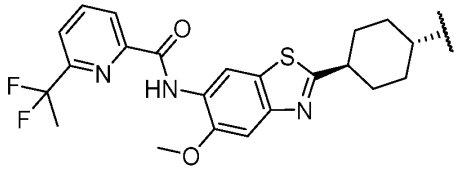
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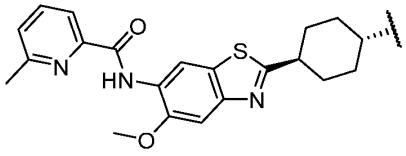
[00181] In some embodiments, L is selected from those depicted in **Table 1**, below.

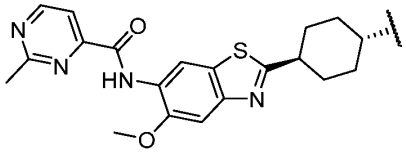
[00182] Without limitation, the point of attachment of L to IRAK and LBM can be, for example when L is  , either  or  .

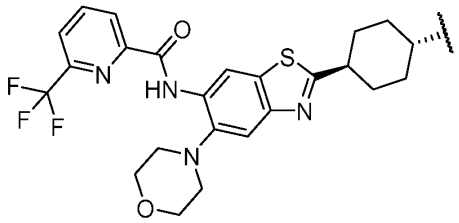
[00183] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

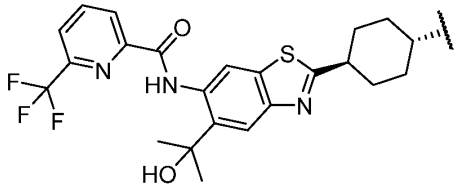
[00184] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

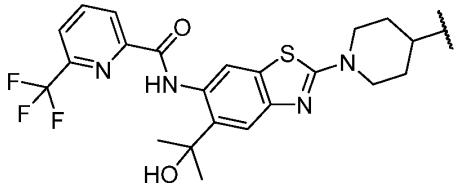
[00185] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

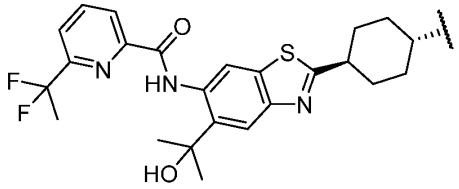
[00186] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

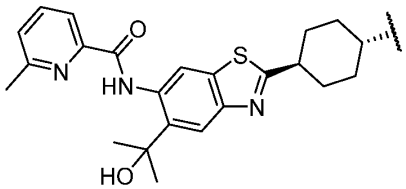
[00187] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

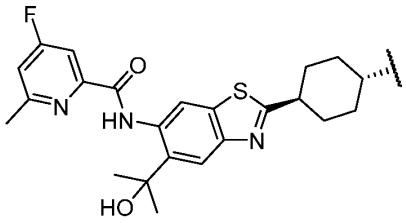
[00188] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

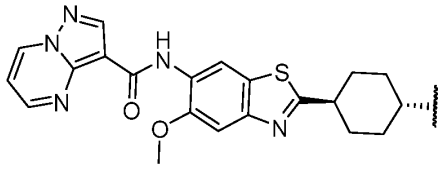
[00189] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

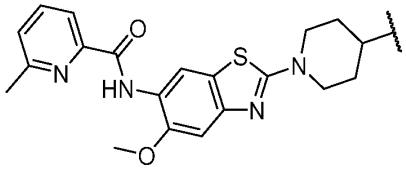
[00190] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

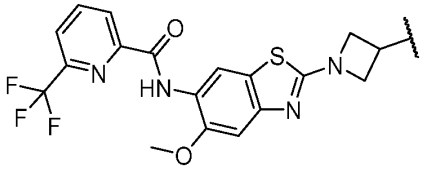
[00191] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

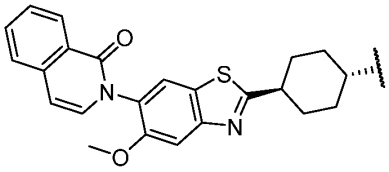
[00192] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

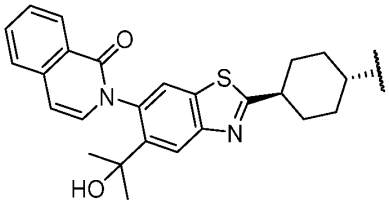
[00193] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

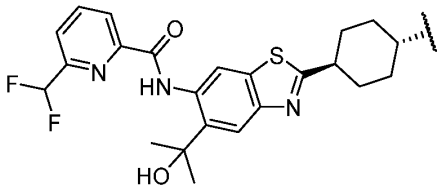
[00194] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

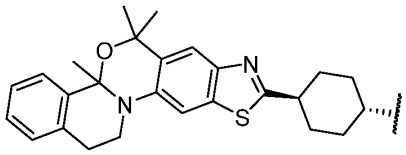
[00195] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

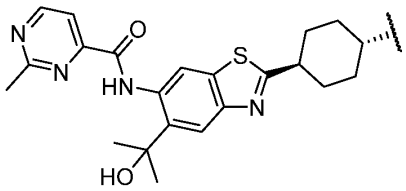
[00196] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

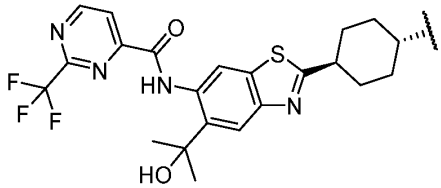
[00197] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

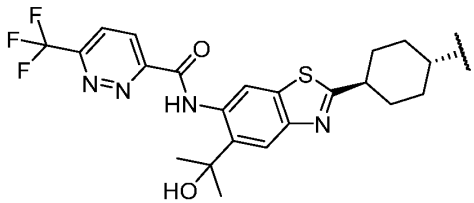
[00198] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

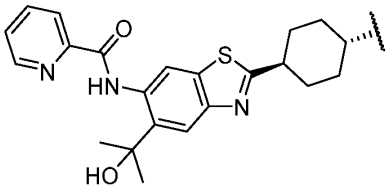
[00199] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

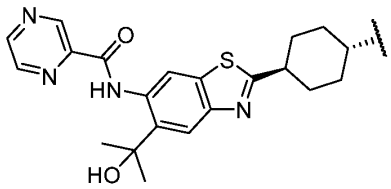
[00200] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

[00201] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

[00202] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

[00203] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

[00204] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

[00205] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

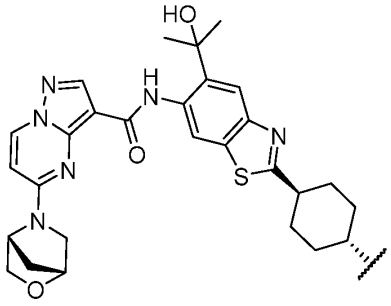
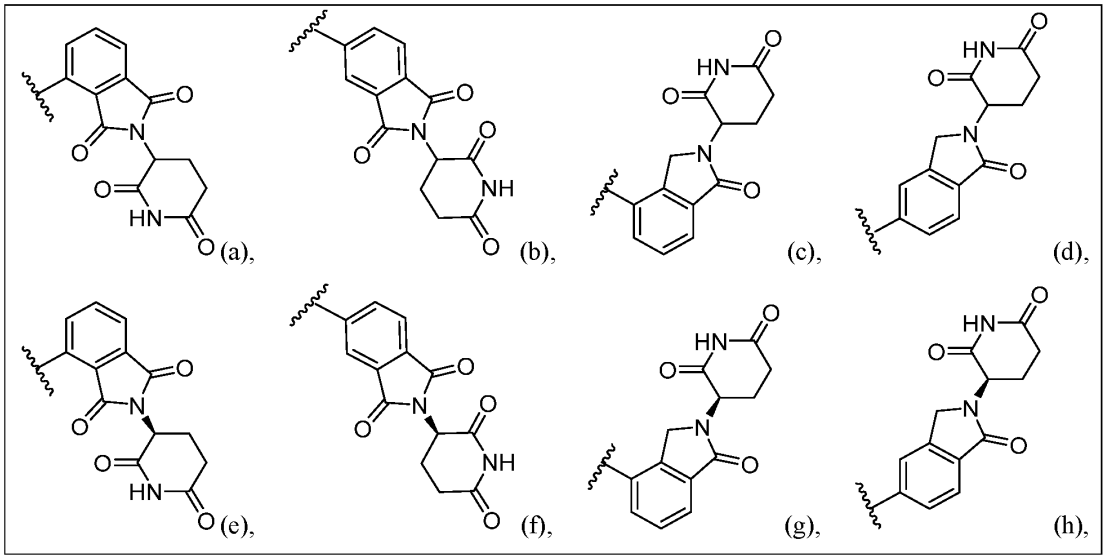
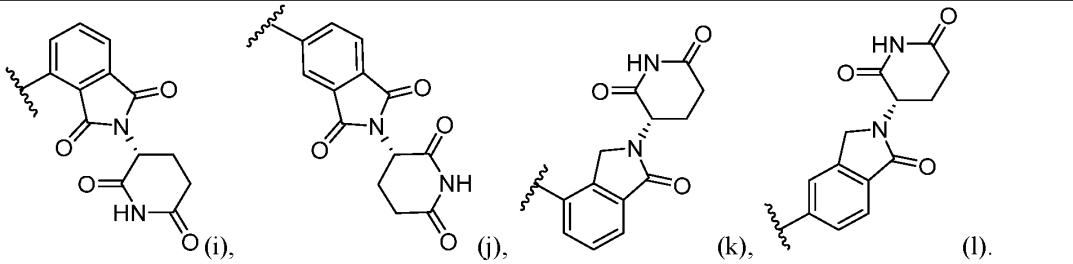
[00206] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein IRAK is  , LBM is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

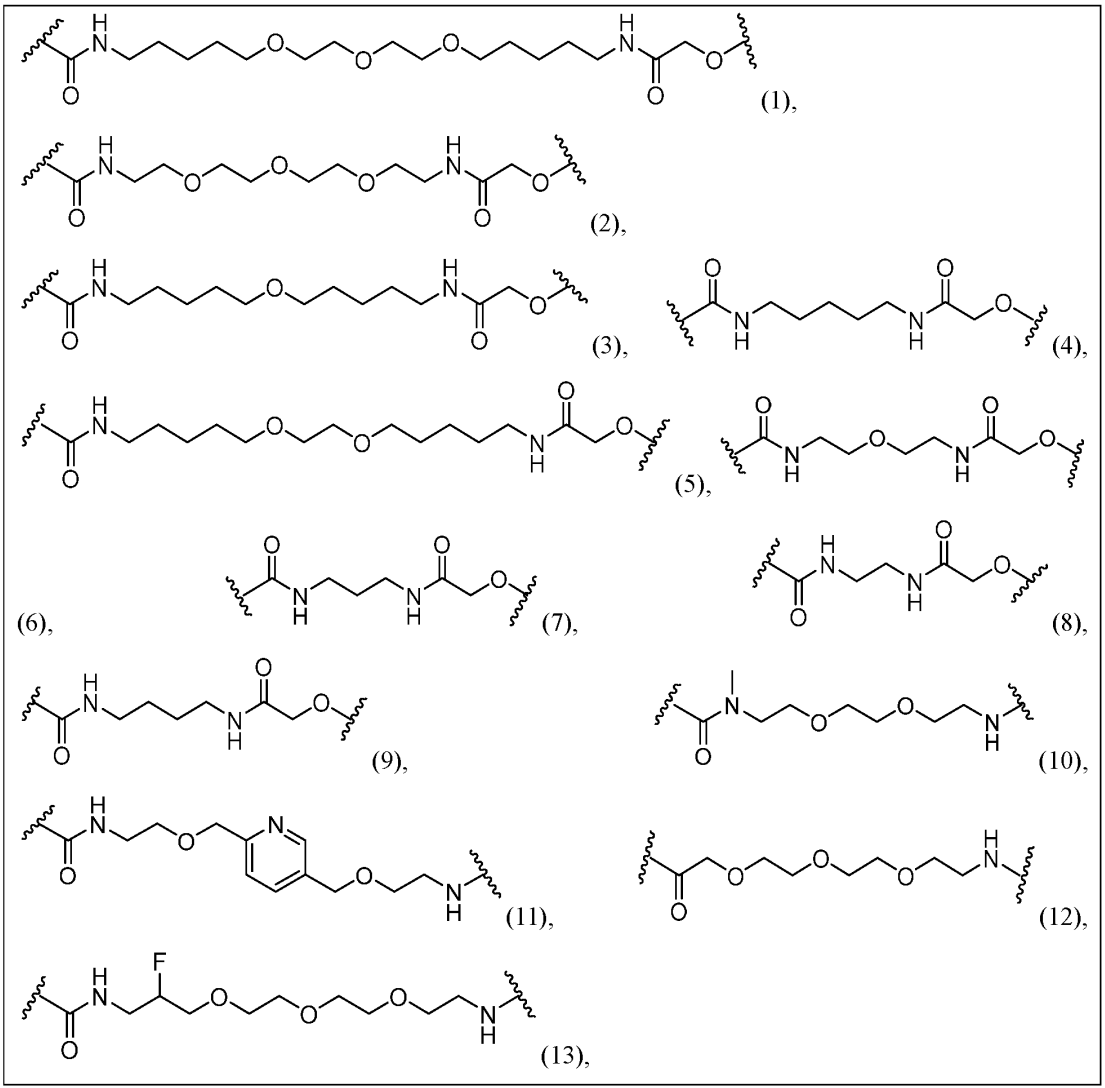
Table A. Exemplified E3 ligases (LBM)



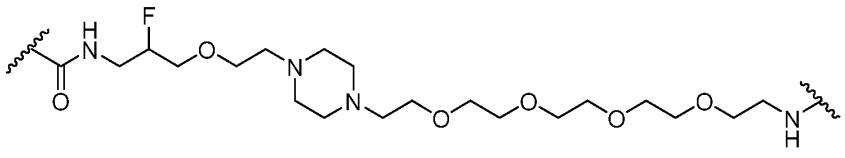


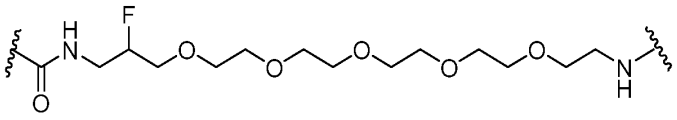
(i), (j), (k), (l).

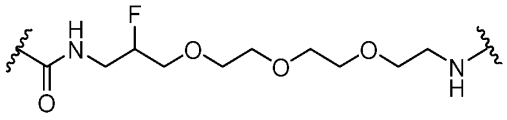
Table B. Exemplified Linkers (L)

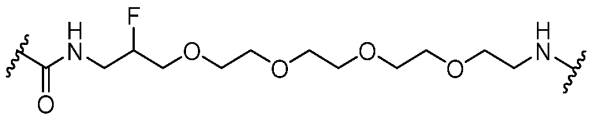


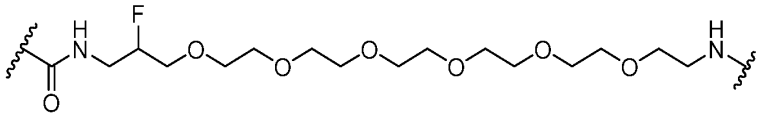
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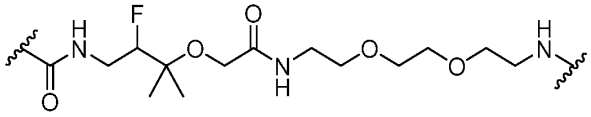

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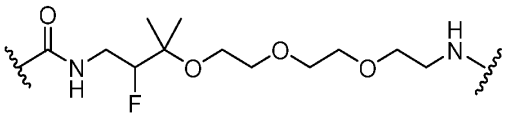

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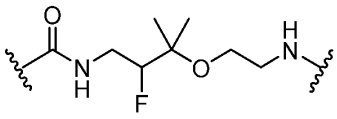

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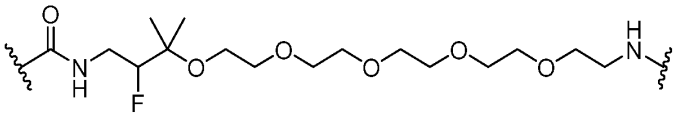

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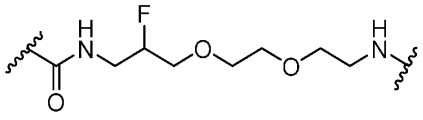

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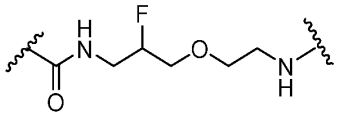

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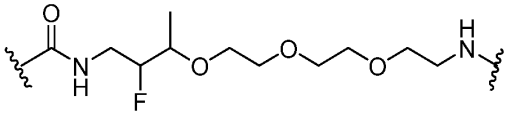

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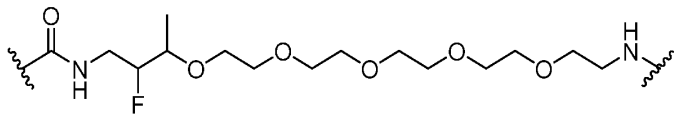

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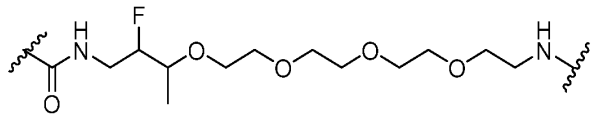

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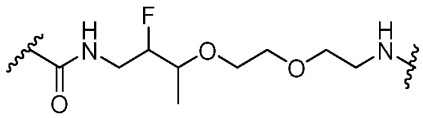

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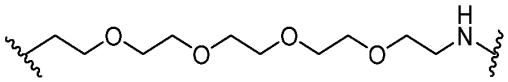

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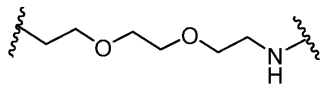

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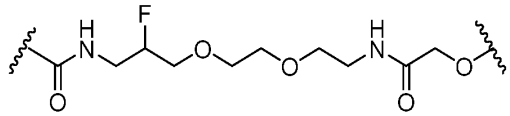

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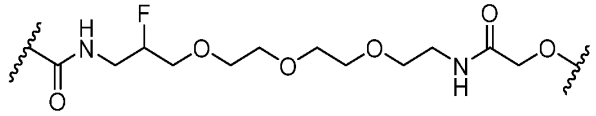


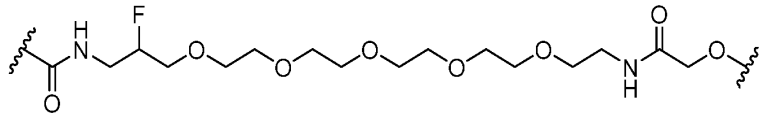

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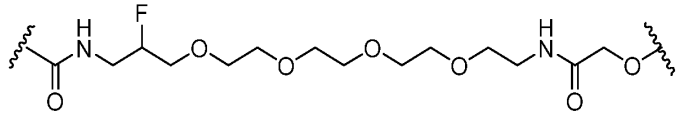

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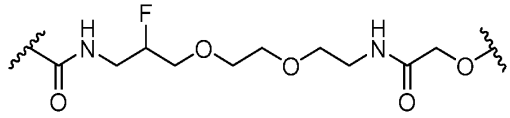

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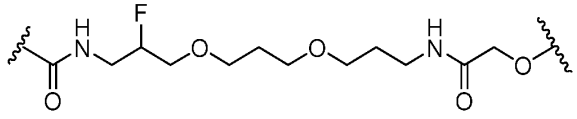
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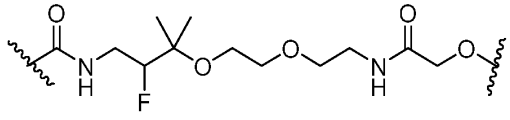

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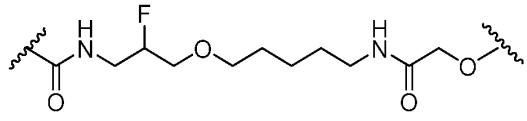

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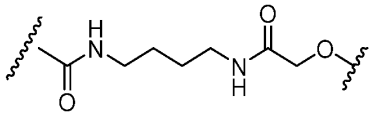

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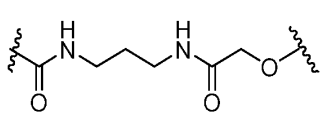

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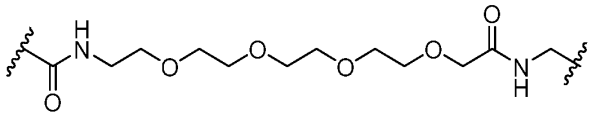

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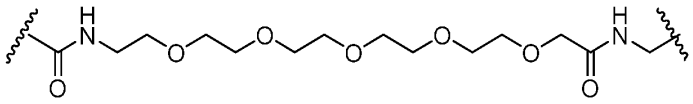

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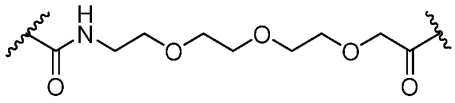

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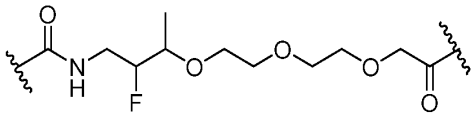

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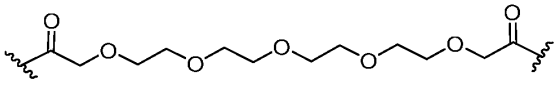

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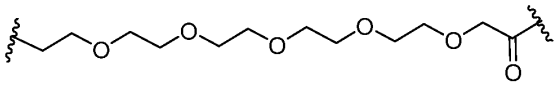

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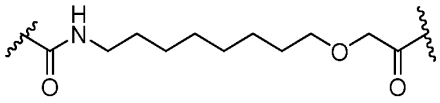

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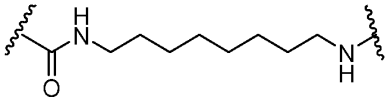

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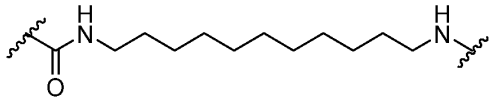

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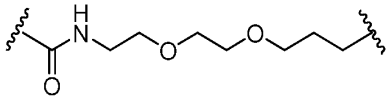

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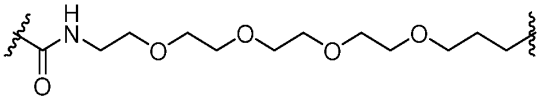


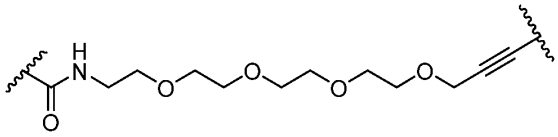
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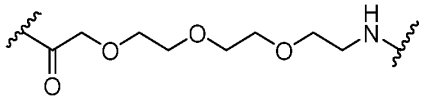

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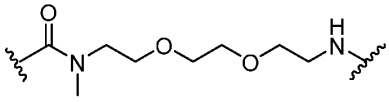

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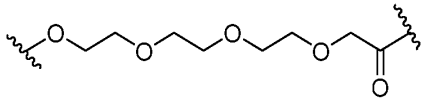

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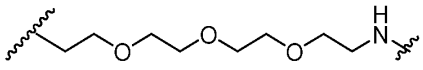

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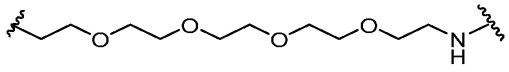


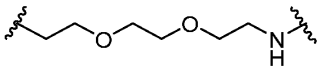
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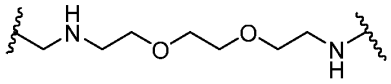

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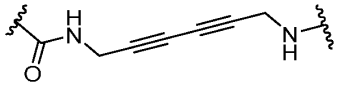

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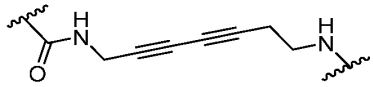

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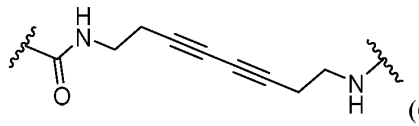

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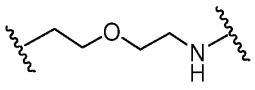

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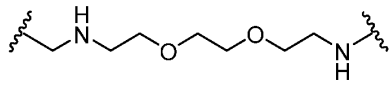

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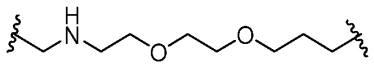

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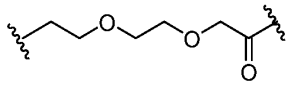

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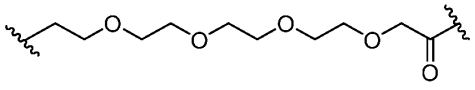

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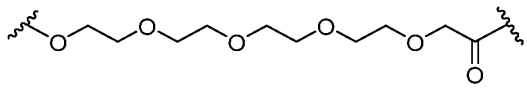

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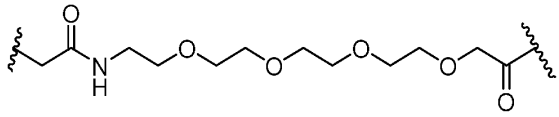

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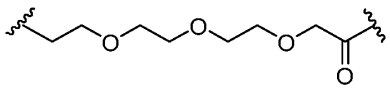

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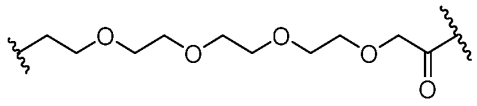

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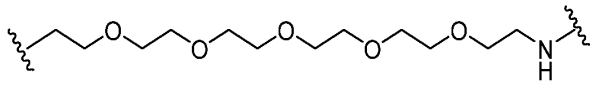

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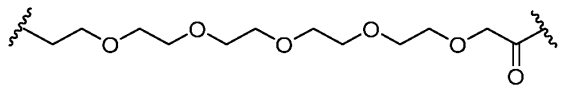

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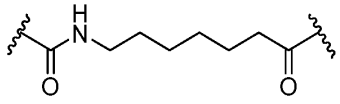

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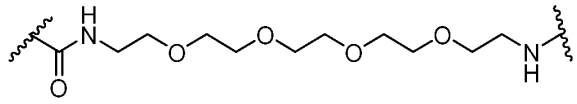

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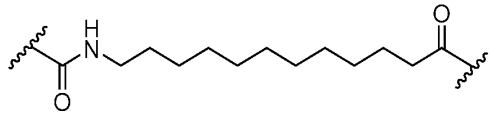

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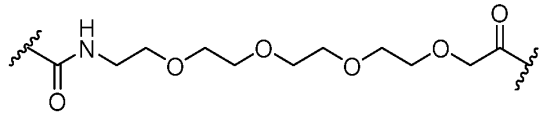

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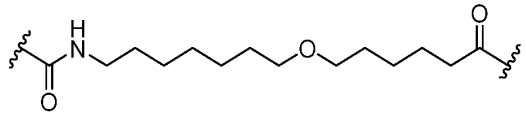

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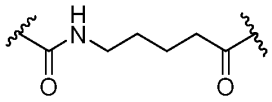

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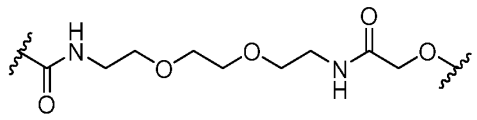

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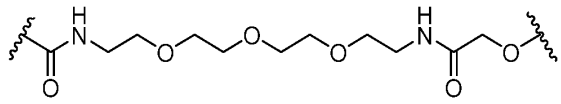

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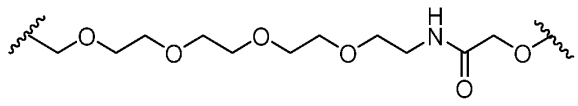

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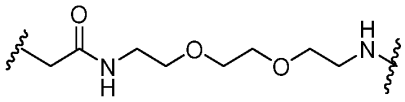

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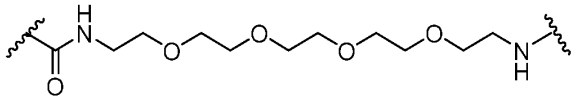

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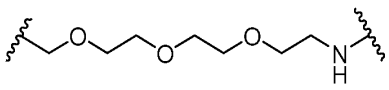

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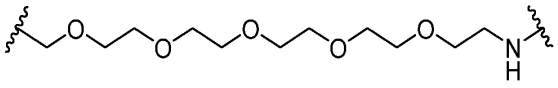

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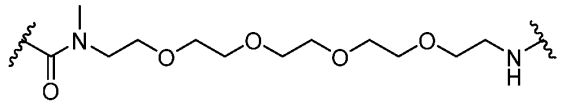


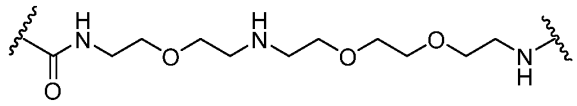

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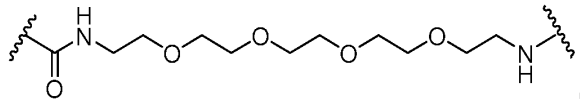

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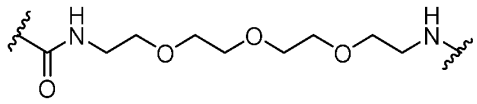

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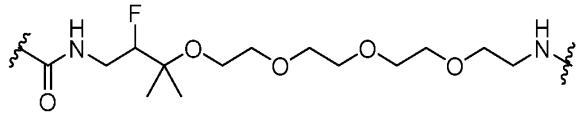
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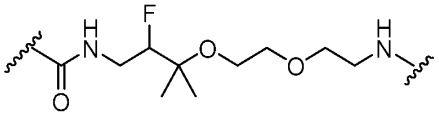

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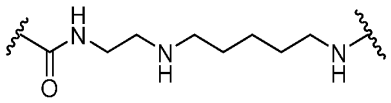

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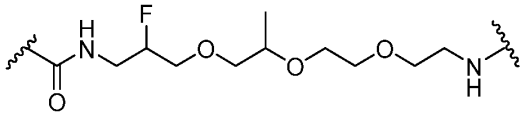

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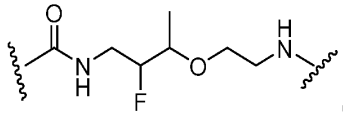

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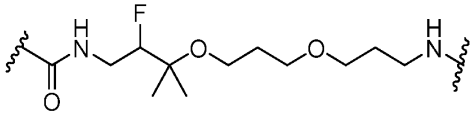


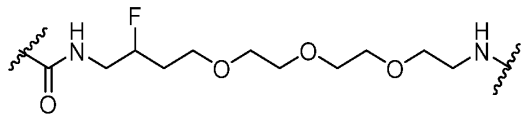

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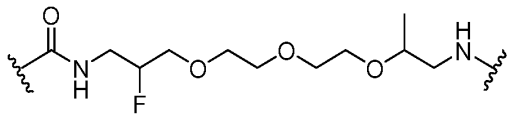
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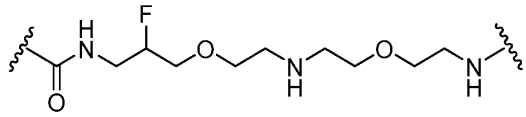

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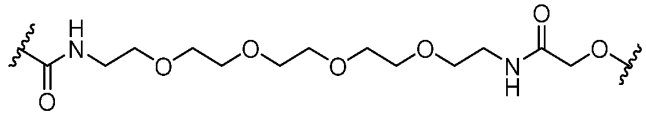

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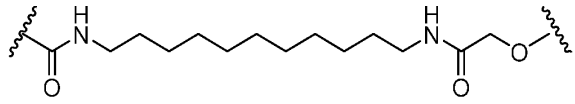

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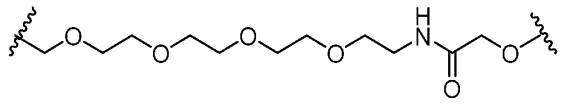

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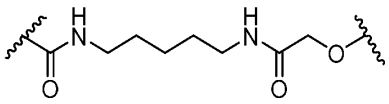

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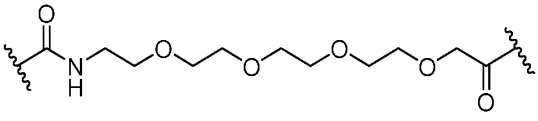

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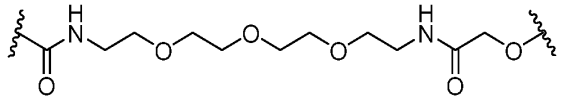

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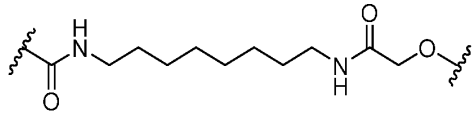

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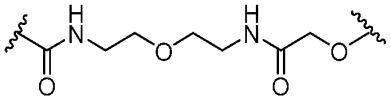

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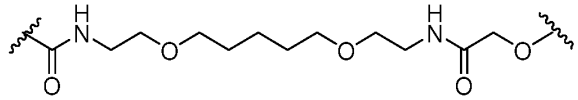


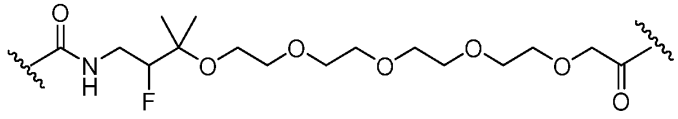

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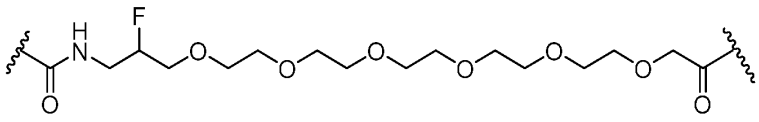

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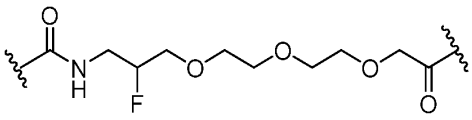

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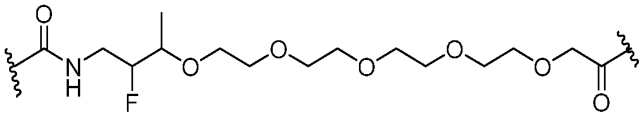

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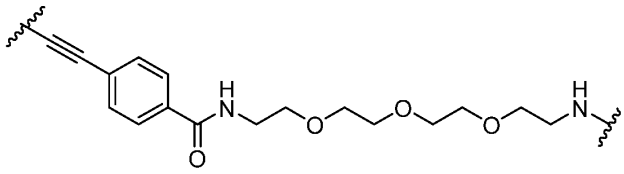

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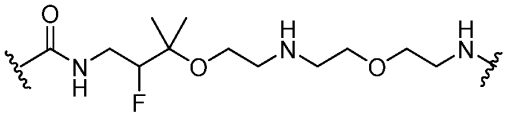

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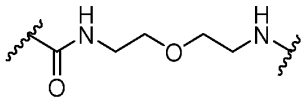

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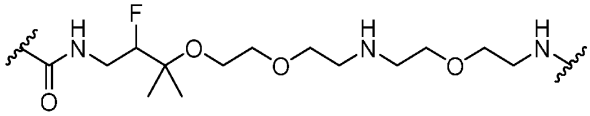

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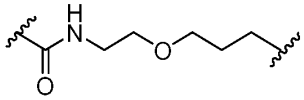

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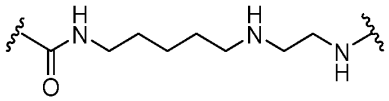

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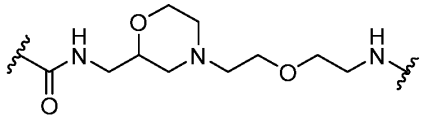

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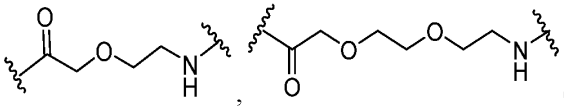

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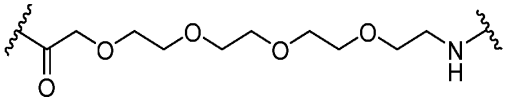

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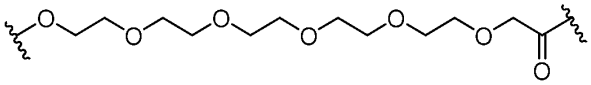

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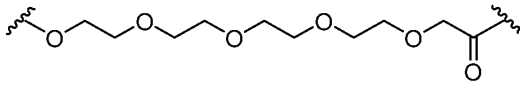

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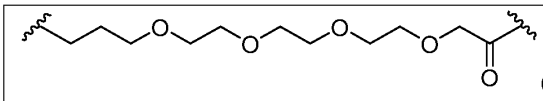

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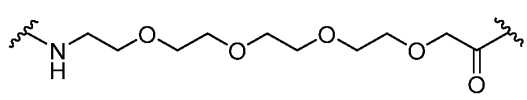

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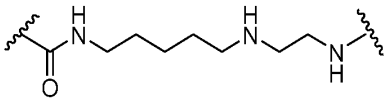

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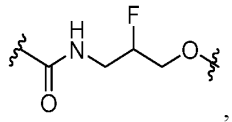

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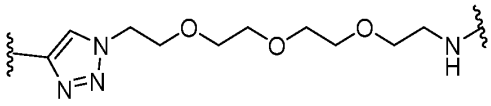

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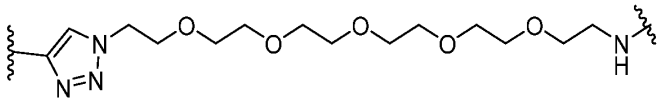

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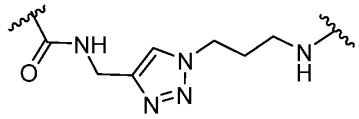

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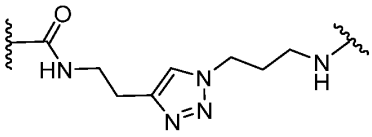

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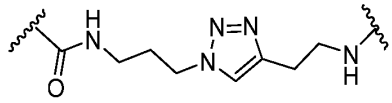

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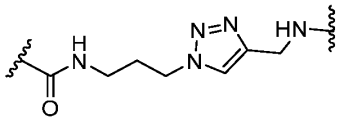

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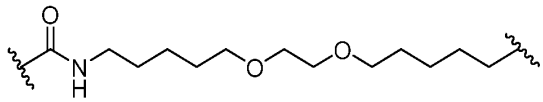

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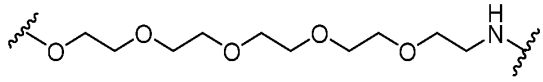

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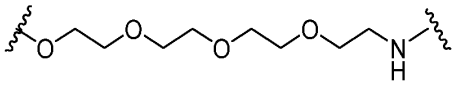

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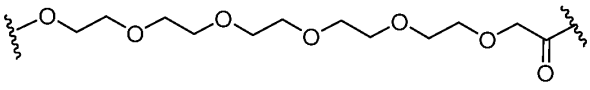

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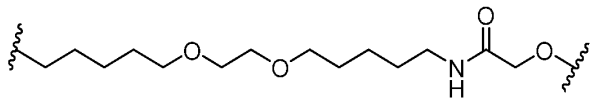

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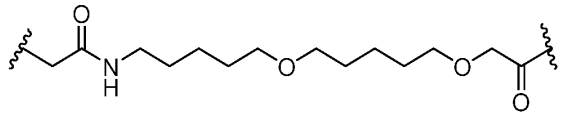

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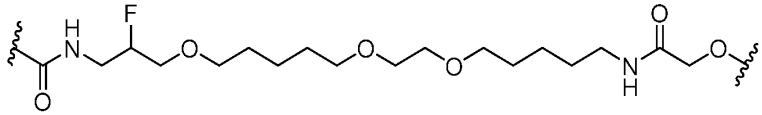

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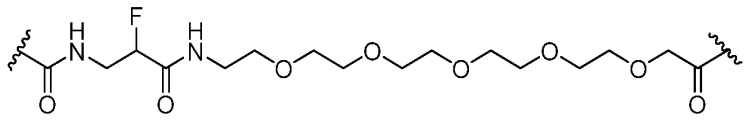


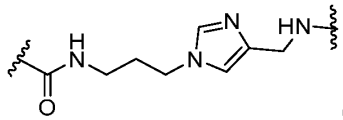

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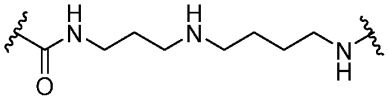

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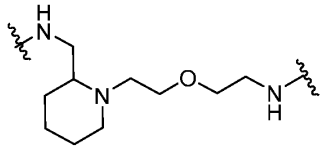

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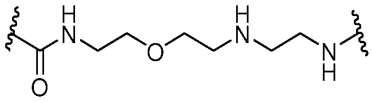

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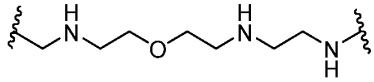

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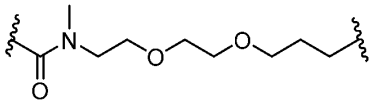

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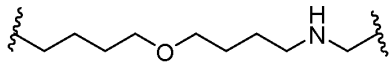

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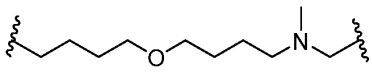

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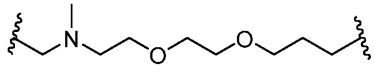

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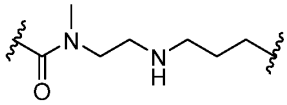

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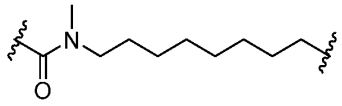

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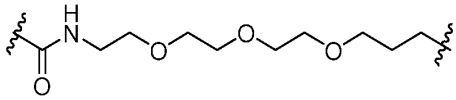

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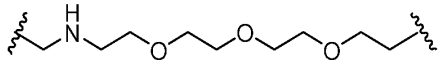

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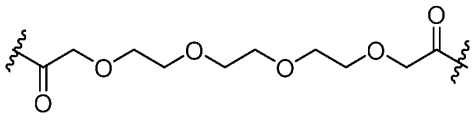

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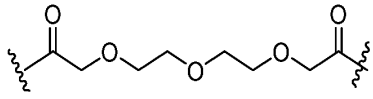

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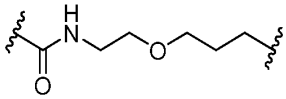

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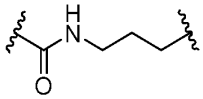

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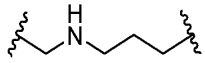

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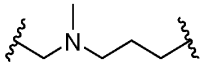

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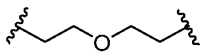

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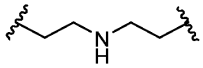

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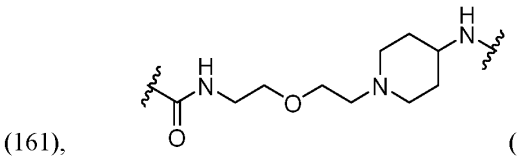

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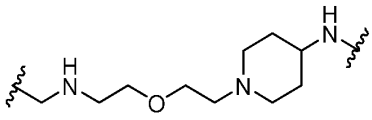

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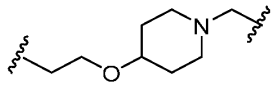

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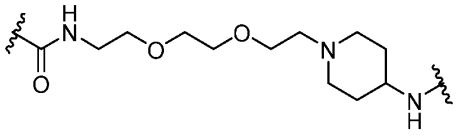


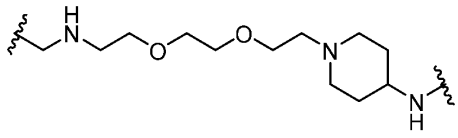

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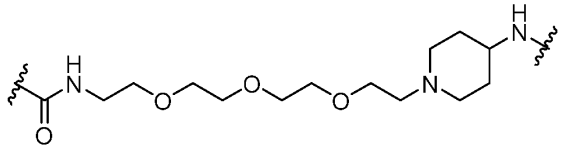
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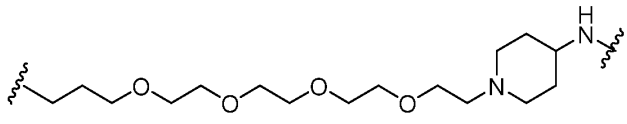

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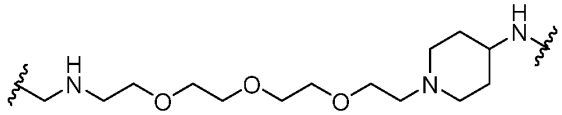

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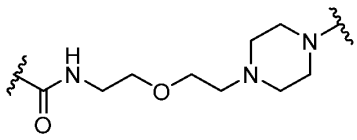

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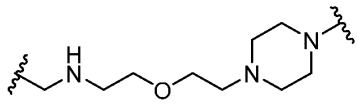

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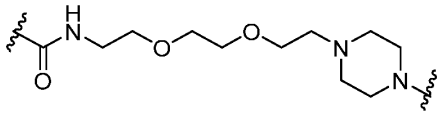

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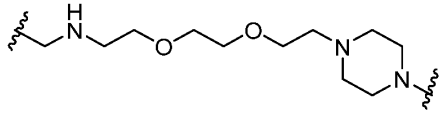

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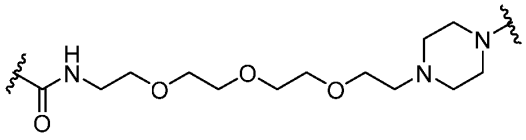

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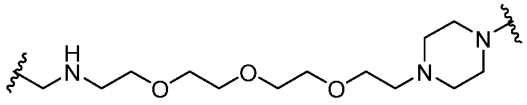

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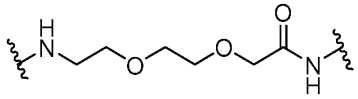

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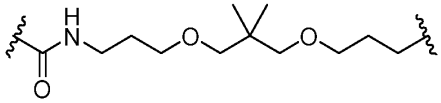

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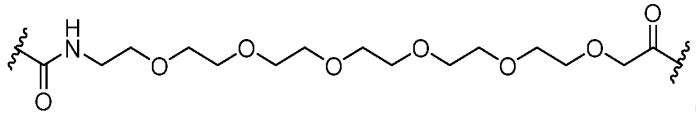

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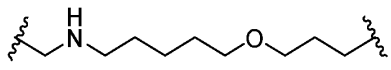

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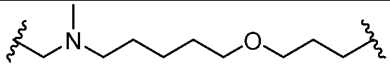

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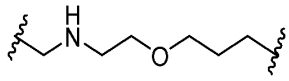

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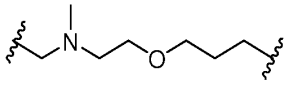

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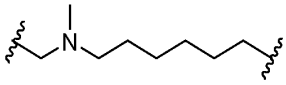

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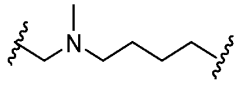

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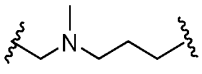

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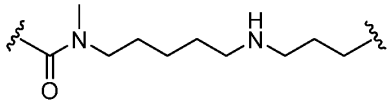

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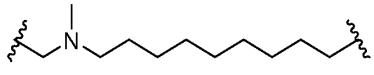

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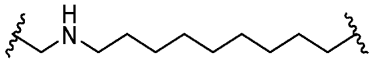

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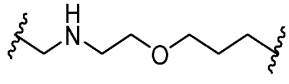

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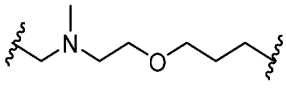

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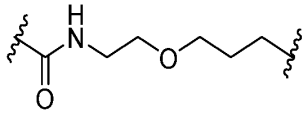

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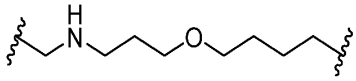

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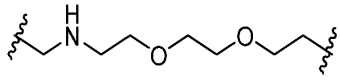

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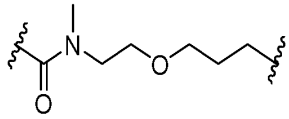

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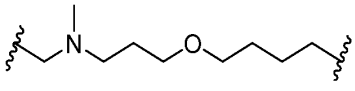

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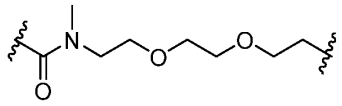

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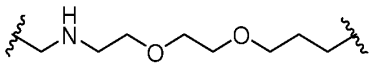

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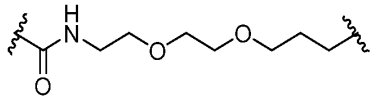

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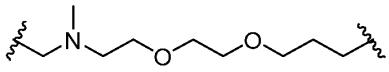

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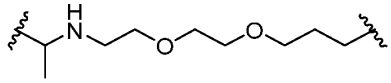

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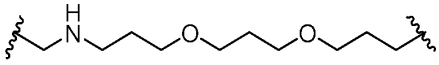

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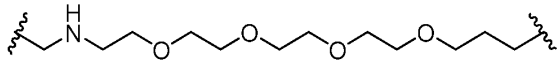

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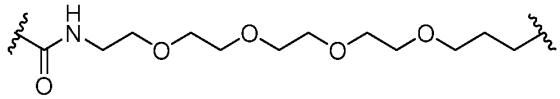

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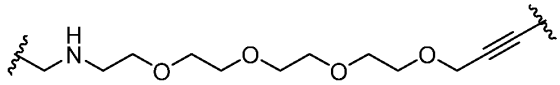

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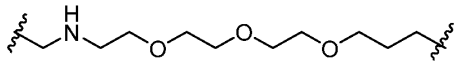

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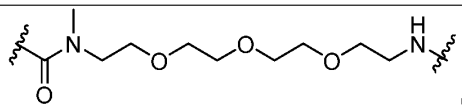

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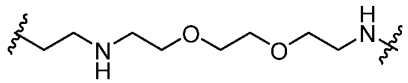

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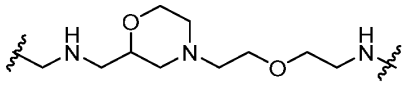

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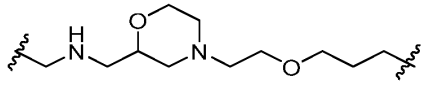

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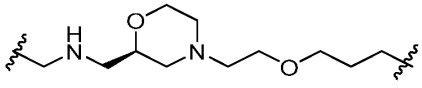

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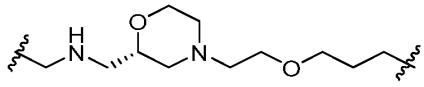

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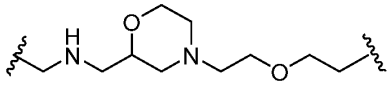

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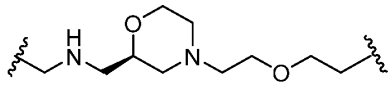

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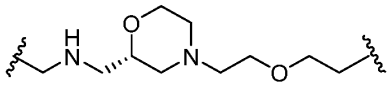

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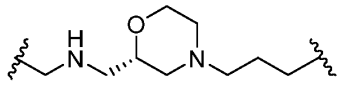

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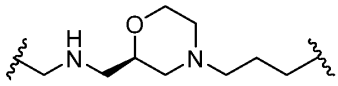

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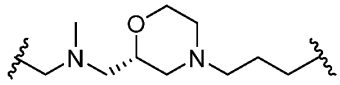

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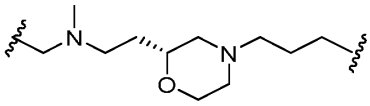

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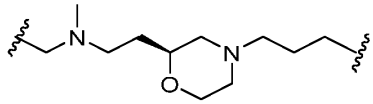

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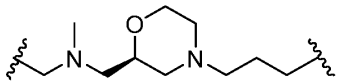

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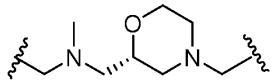

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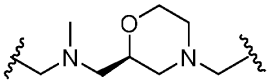

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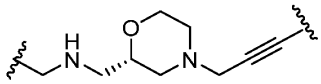

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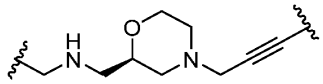

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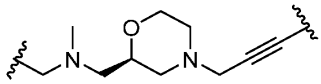

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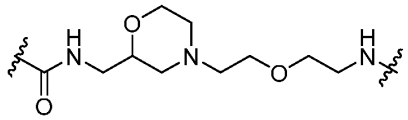

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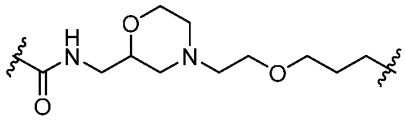

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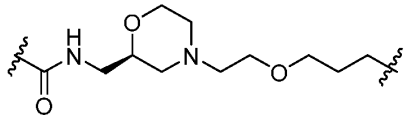

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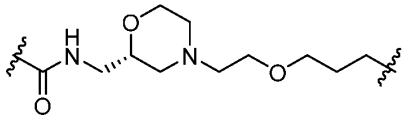

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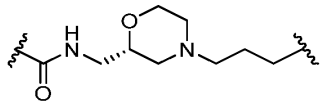

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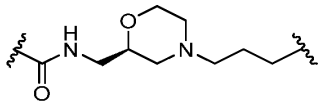

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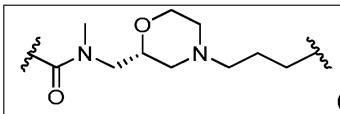

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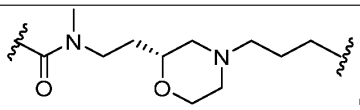

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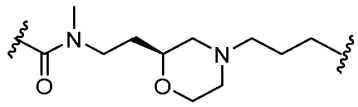

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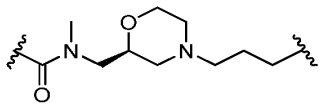

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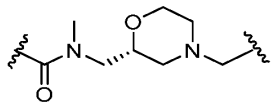

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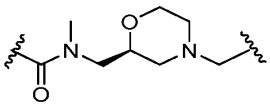

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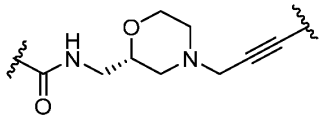

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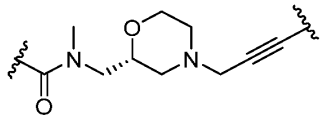

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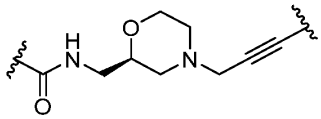

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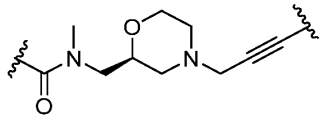

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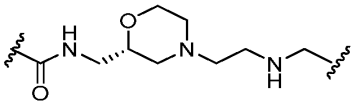

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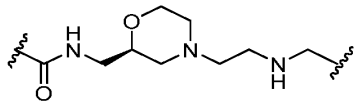

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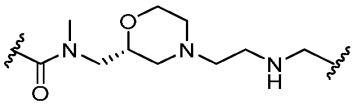

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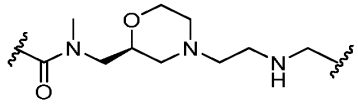

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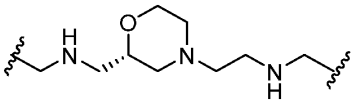

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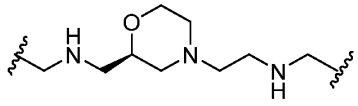

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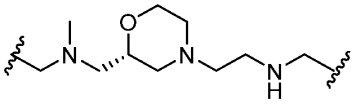

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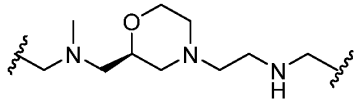

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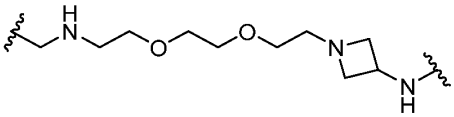

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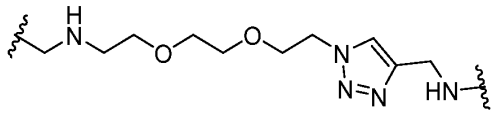

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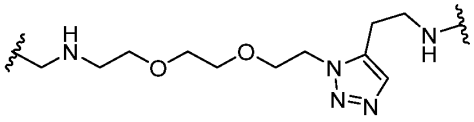

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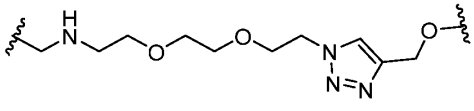

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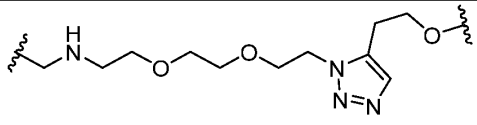
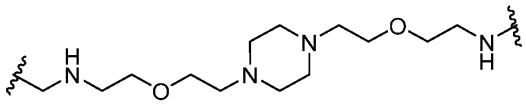
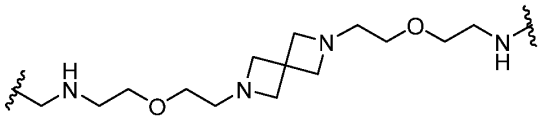
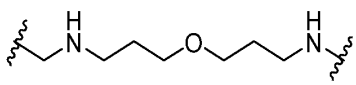
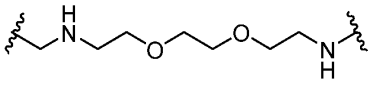
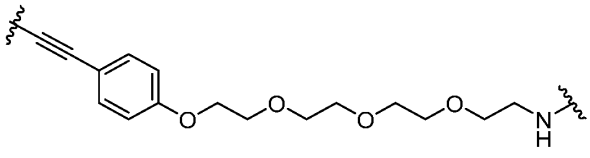
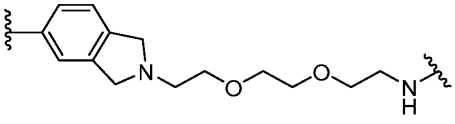
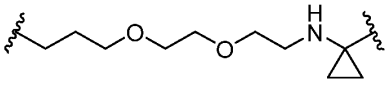
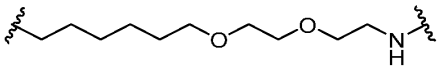
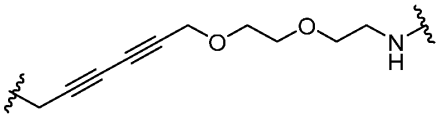
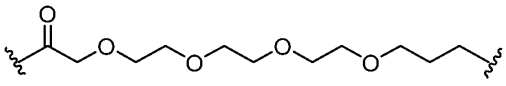
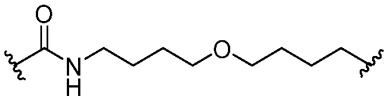
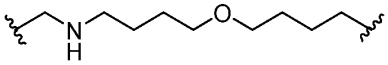
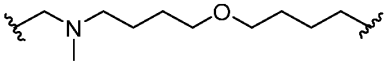
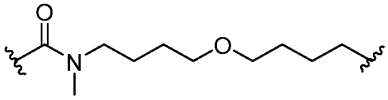
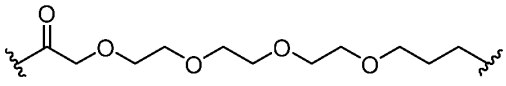
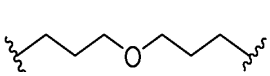
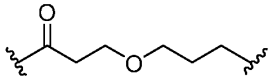
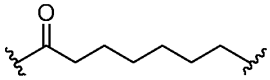
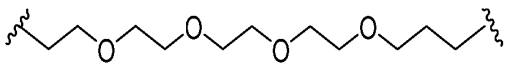
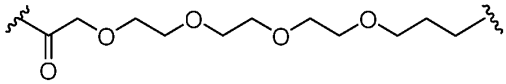

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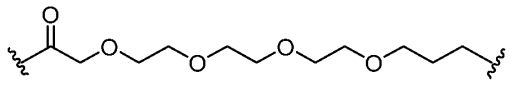

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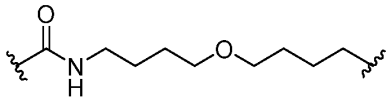


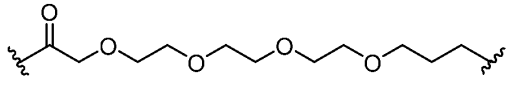

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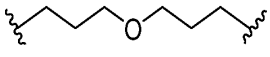
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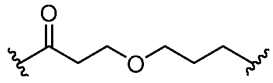

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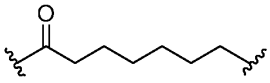

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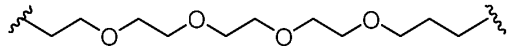

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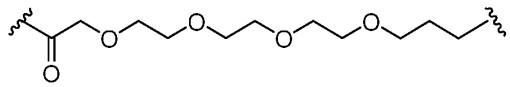

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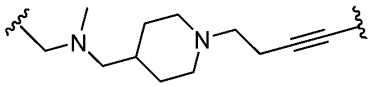

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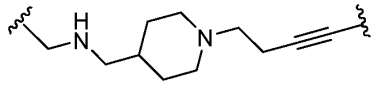

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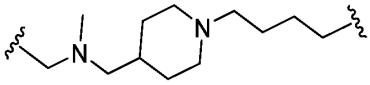

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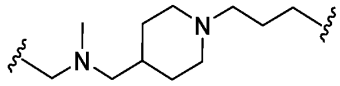

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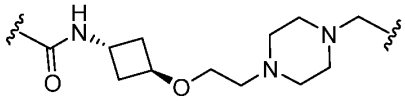

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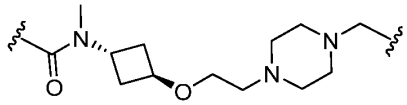

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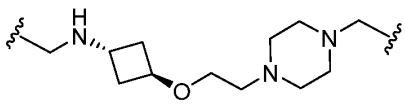

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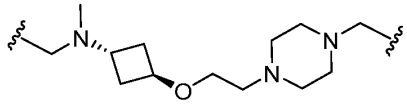

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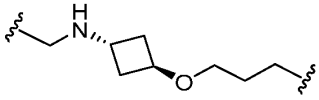

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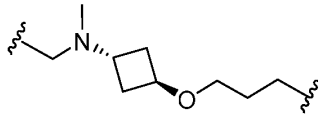

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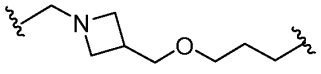

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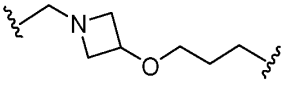

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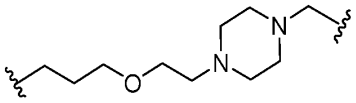

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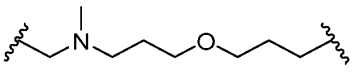

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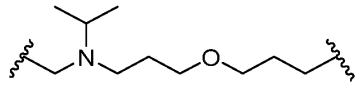

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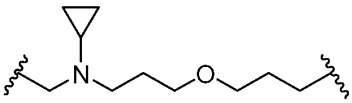


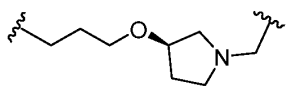

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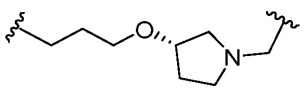
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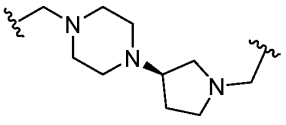

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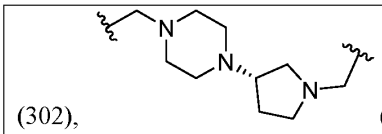
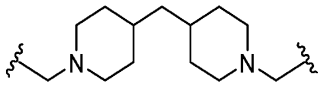
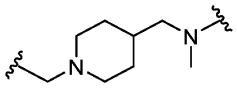
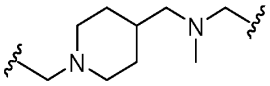
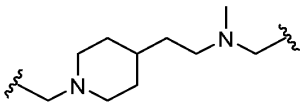
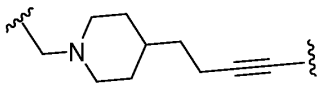
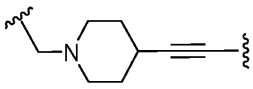
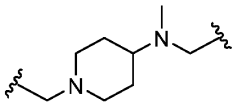
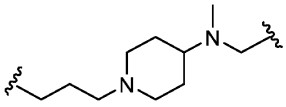
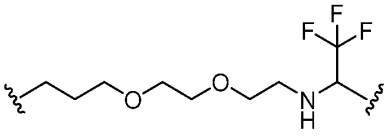
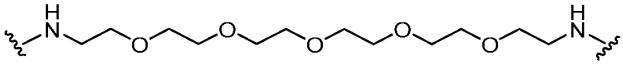
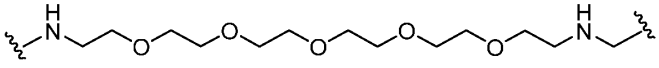
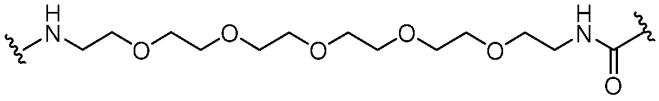
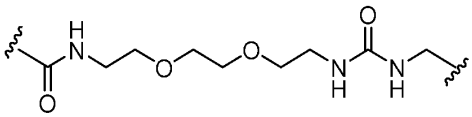
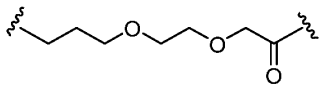
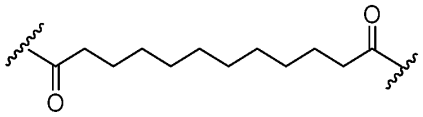
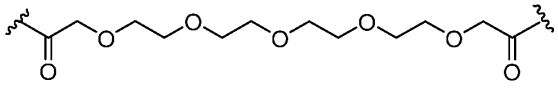
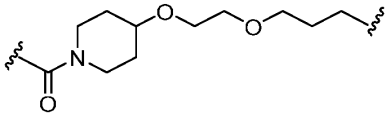
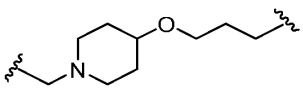
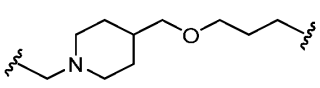
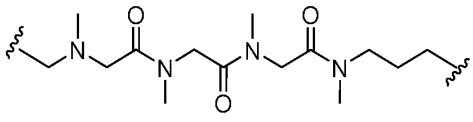

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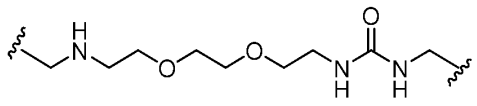

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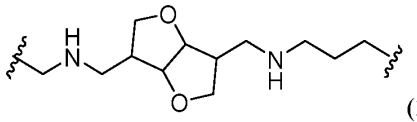

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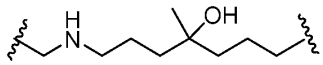

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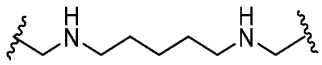


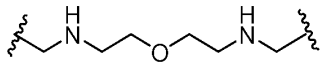

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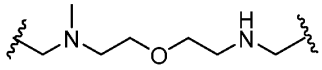

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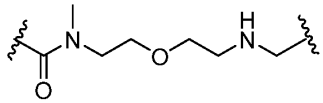

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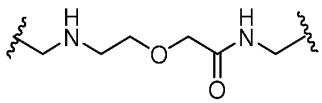

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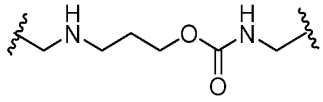

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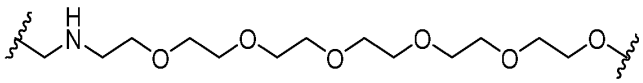

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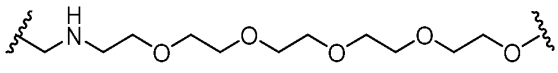

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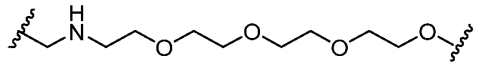

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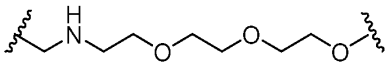

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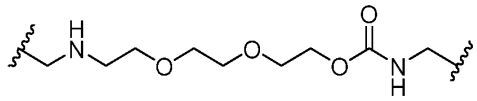

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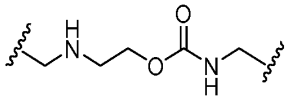

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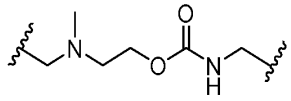

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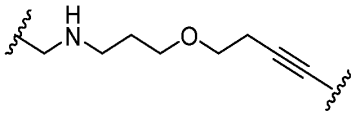

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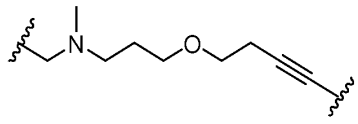

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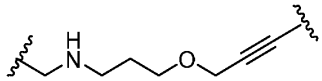

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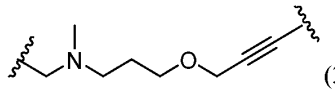

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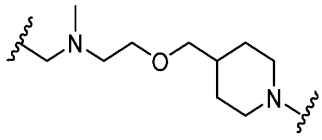

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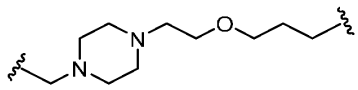

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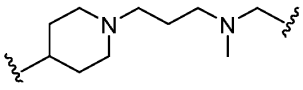

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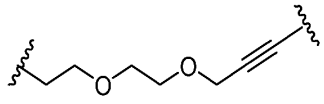
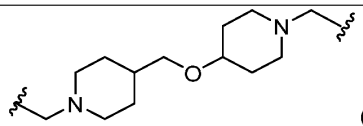
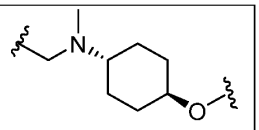
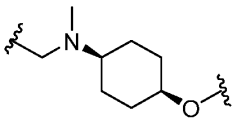
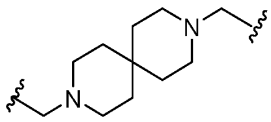
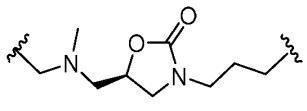
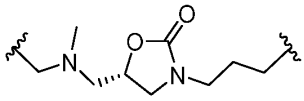
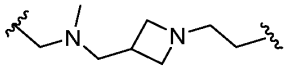
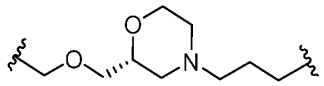
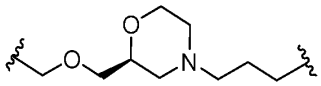
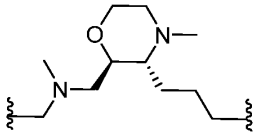
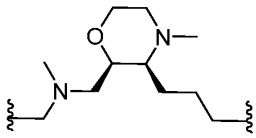
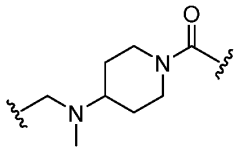
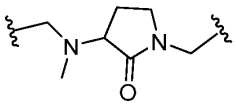
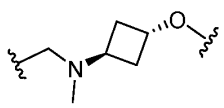
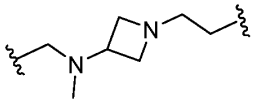
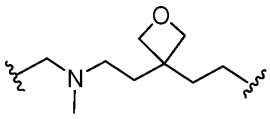
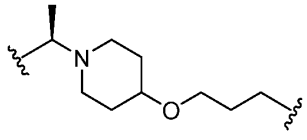
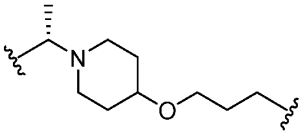
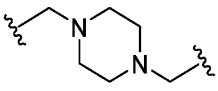
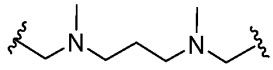
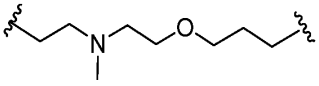
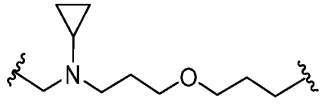
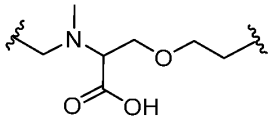
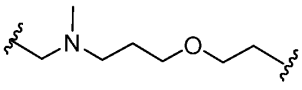
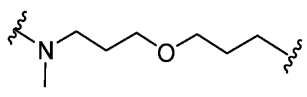
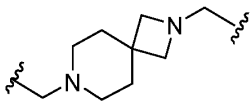
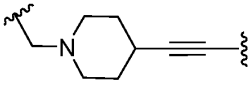

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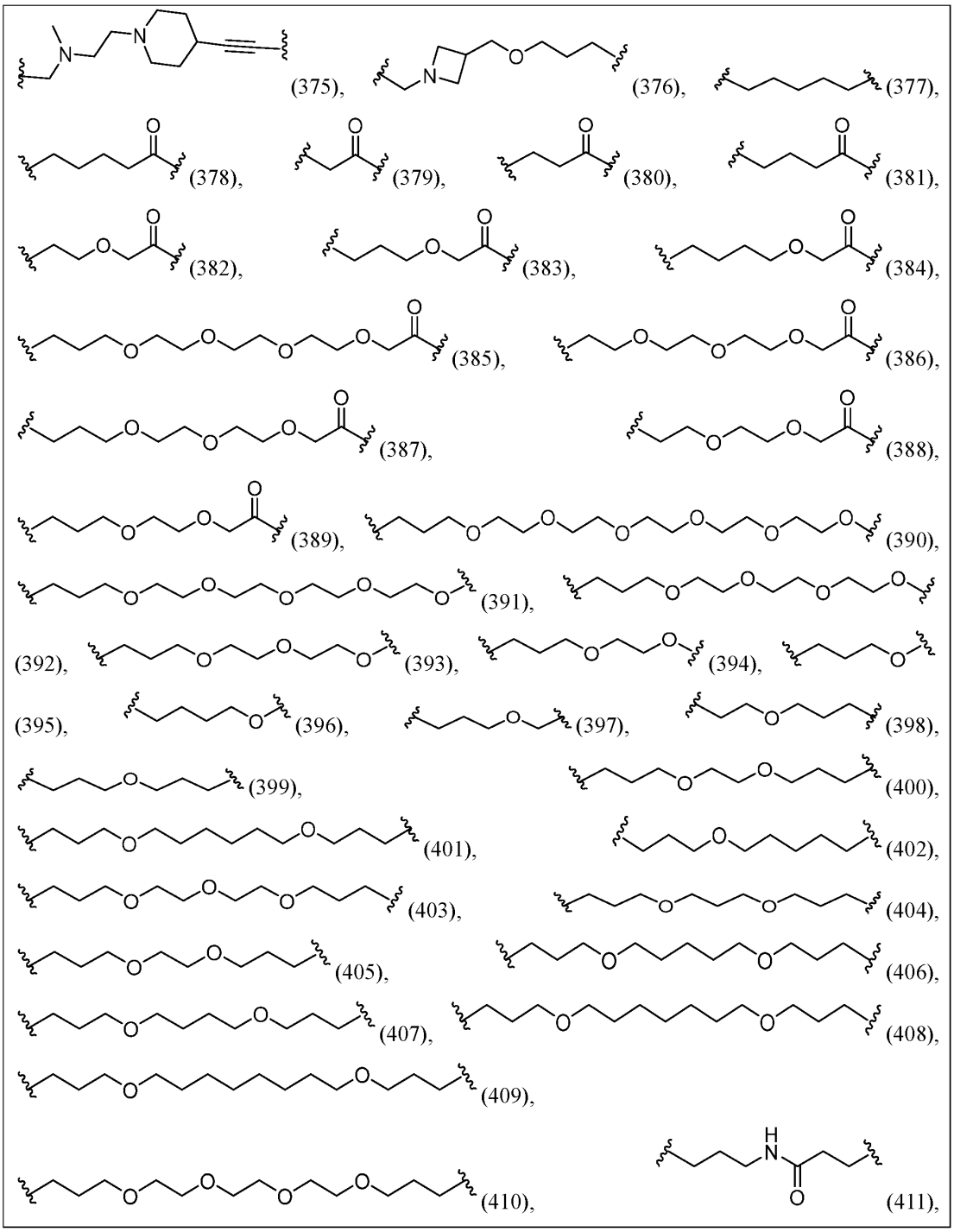

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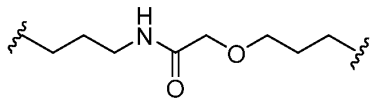

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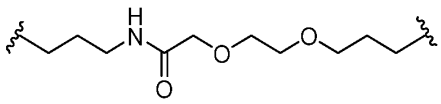

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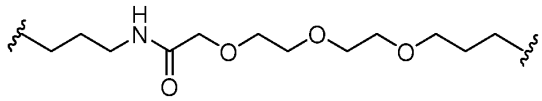

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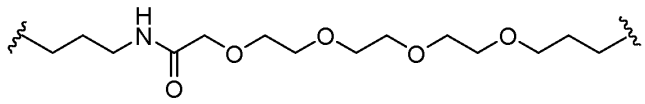

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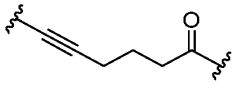

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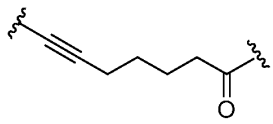

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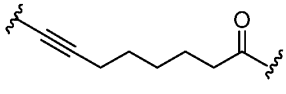

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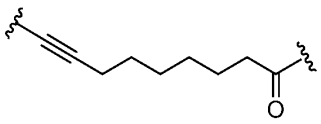

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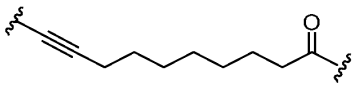

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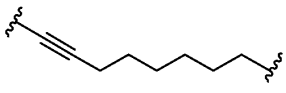

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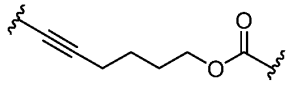

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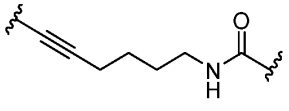

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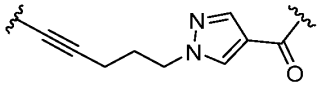

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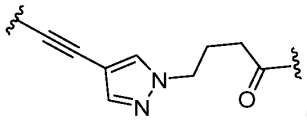

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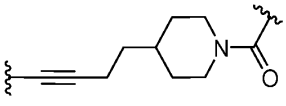

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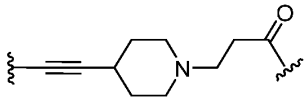

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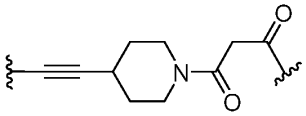

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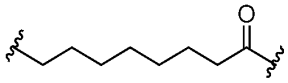

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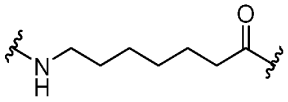

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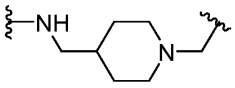

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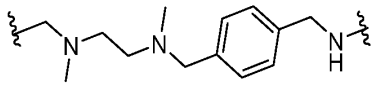

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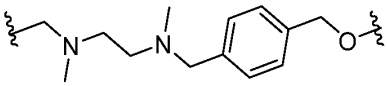

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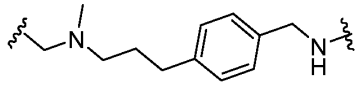

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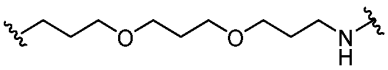

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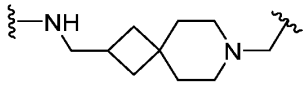

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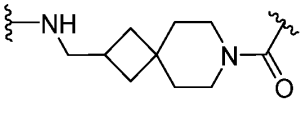

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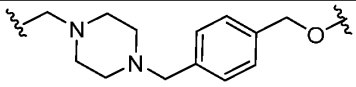

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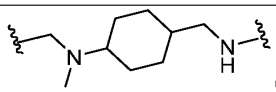

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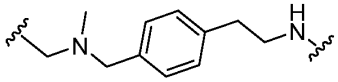

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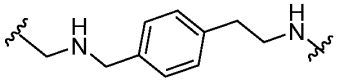

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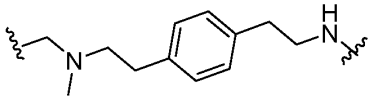

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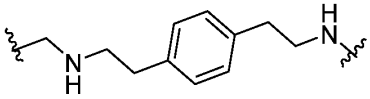

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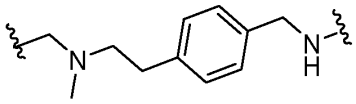

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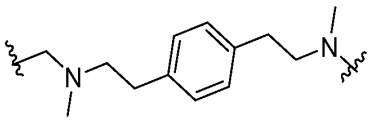

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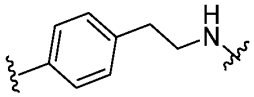

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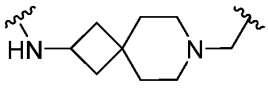

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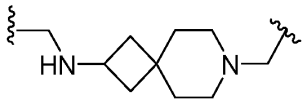

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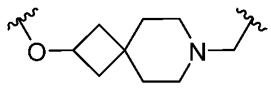

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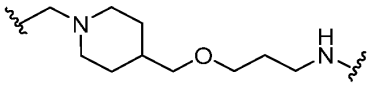

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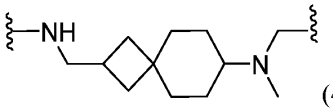

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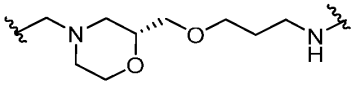

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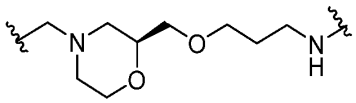

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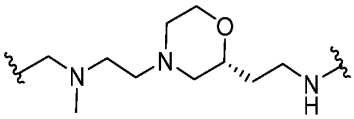

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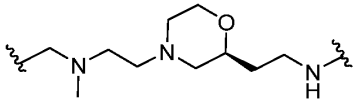

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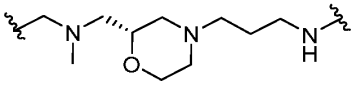

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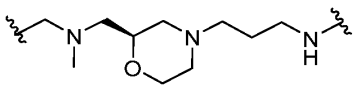

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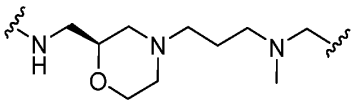

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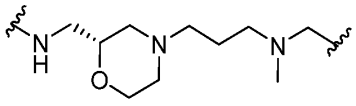

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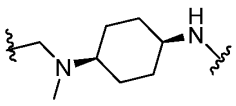

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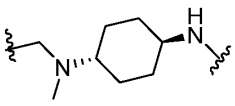

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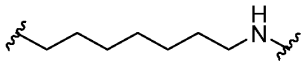

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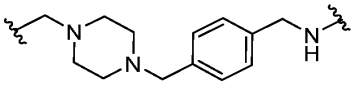

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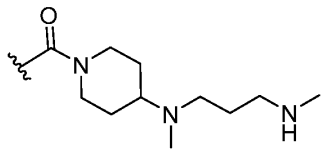

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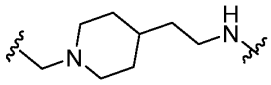

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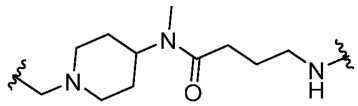

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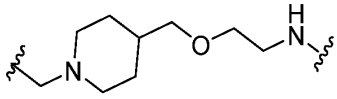

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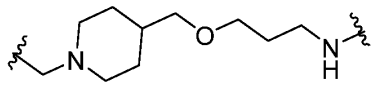

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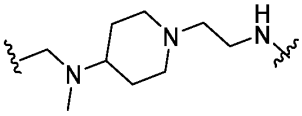

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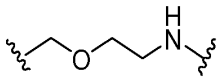

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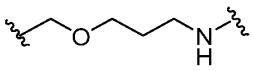

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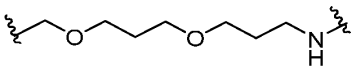

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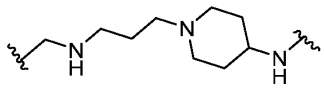

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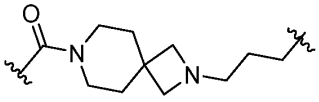


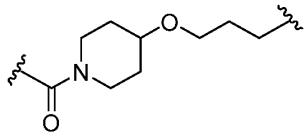
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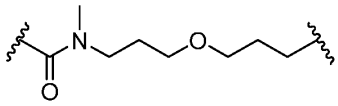

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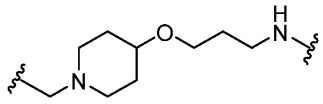

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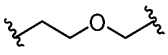

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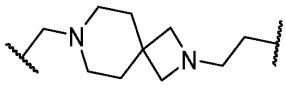

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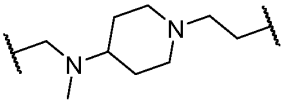

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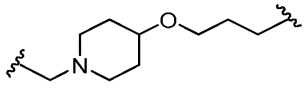

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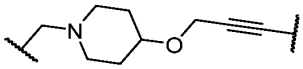

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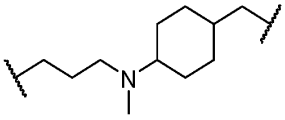

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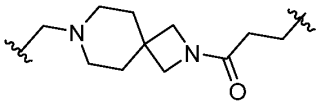

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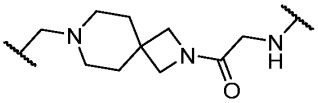

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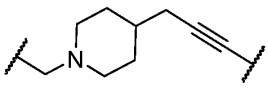


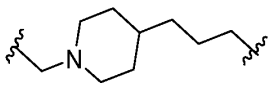
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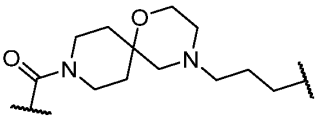

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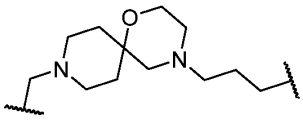

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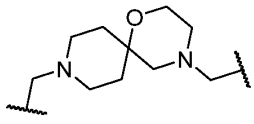

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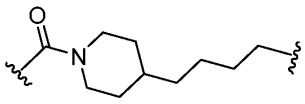
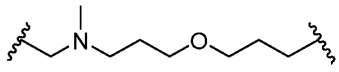

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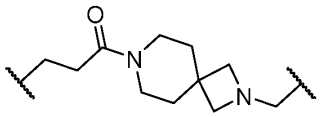
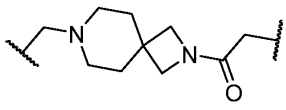

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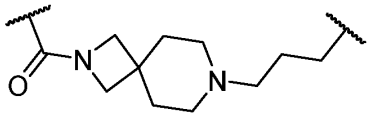
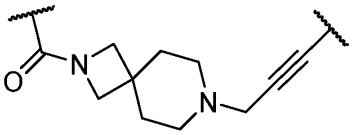

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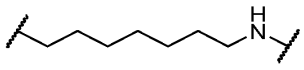
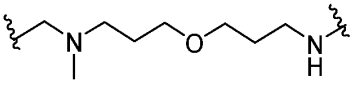

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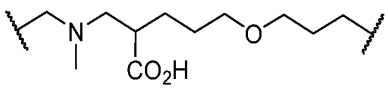
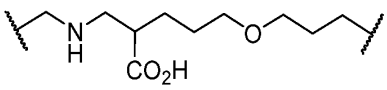


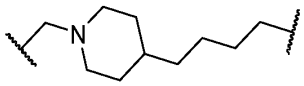
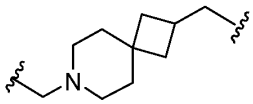
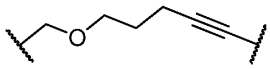
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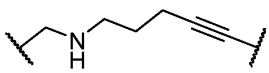
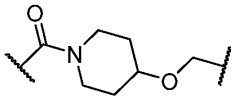
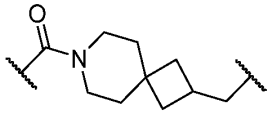
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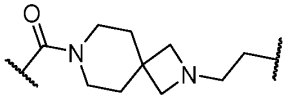
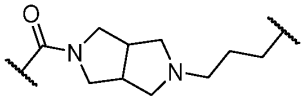
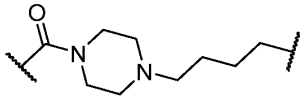
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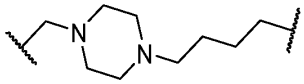
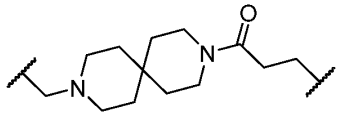
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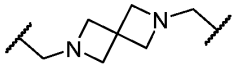
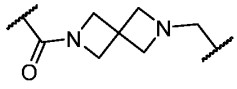
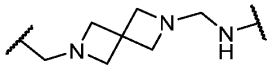
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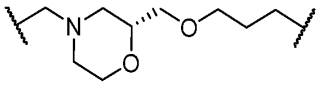
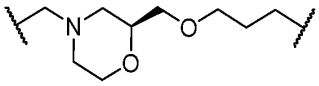
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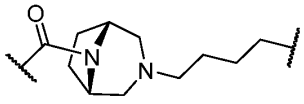
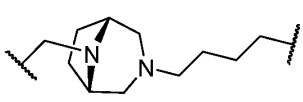
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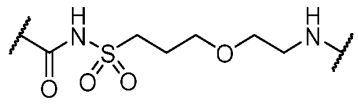
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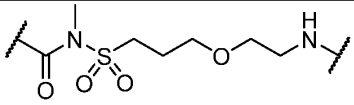
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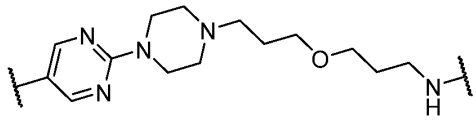
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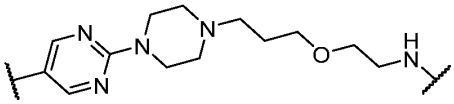
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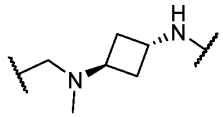
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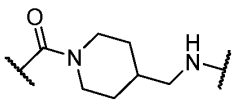

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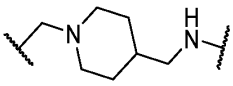

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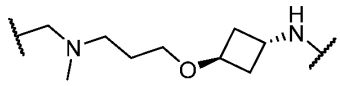

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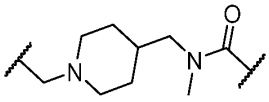

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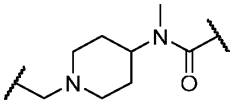

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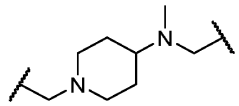

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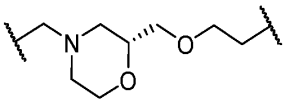

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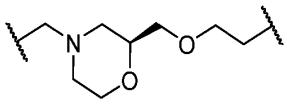

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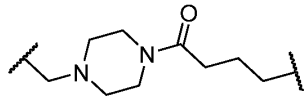

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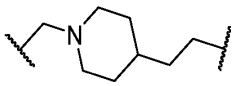

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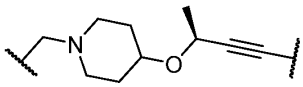

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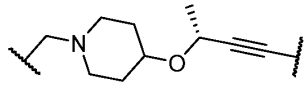

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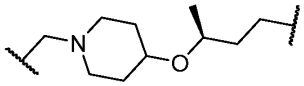

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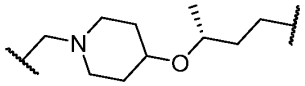

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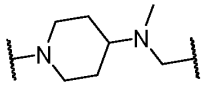

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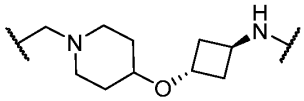

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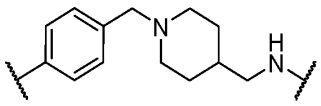

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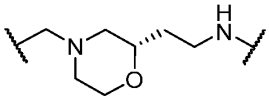

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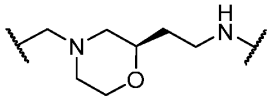

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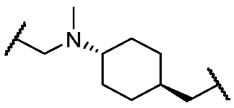

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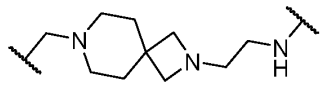

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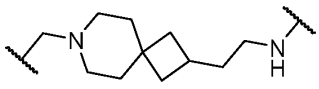

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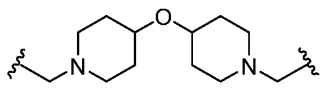

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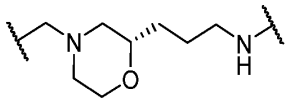

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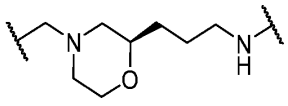

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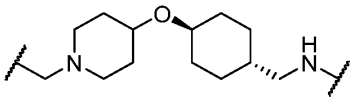

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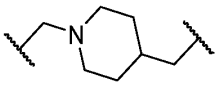

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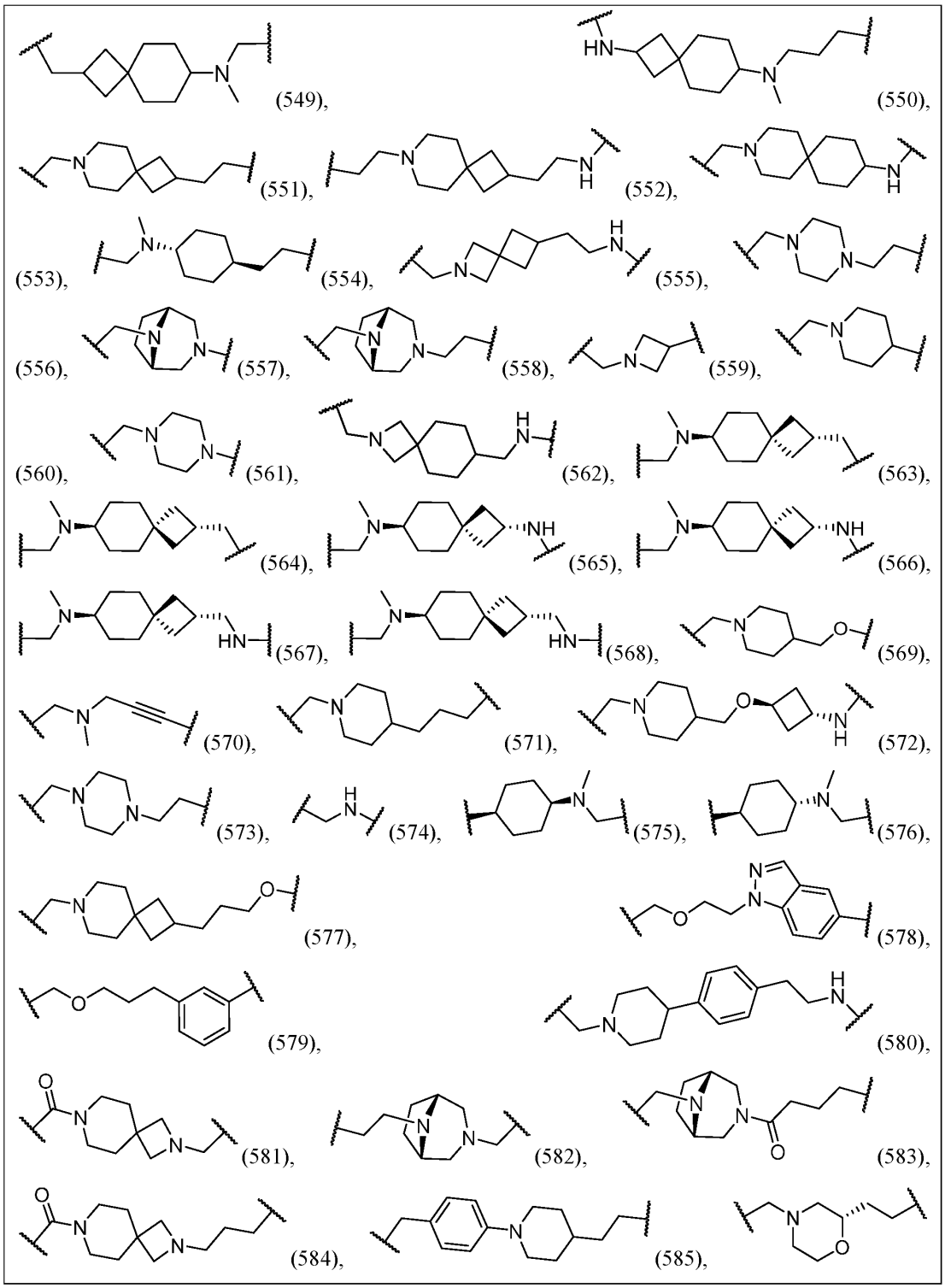

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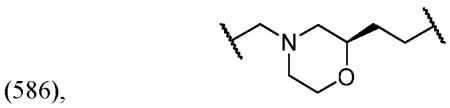

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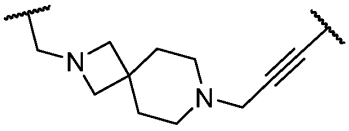

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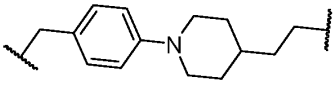

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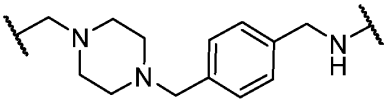

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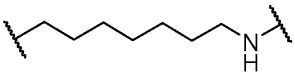

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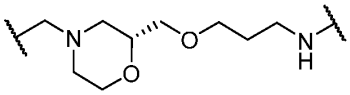

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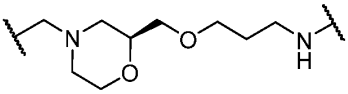

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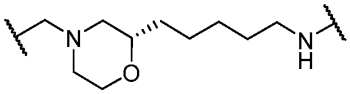

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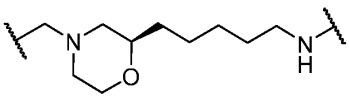

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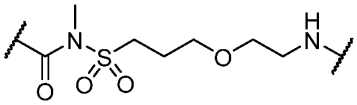

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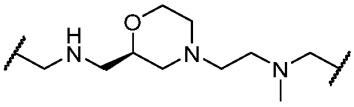

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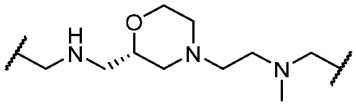

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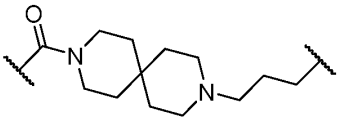

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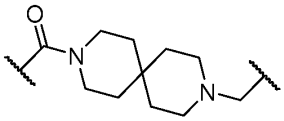

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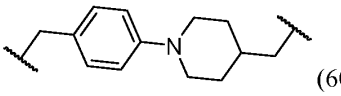

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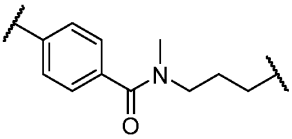

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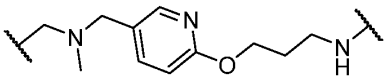

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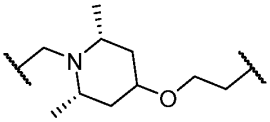

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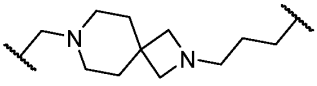

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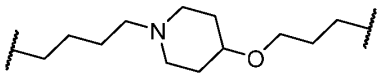

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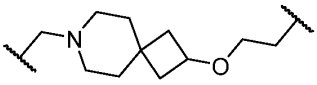

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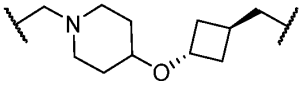

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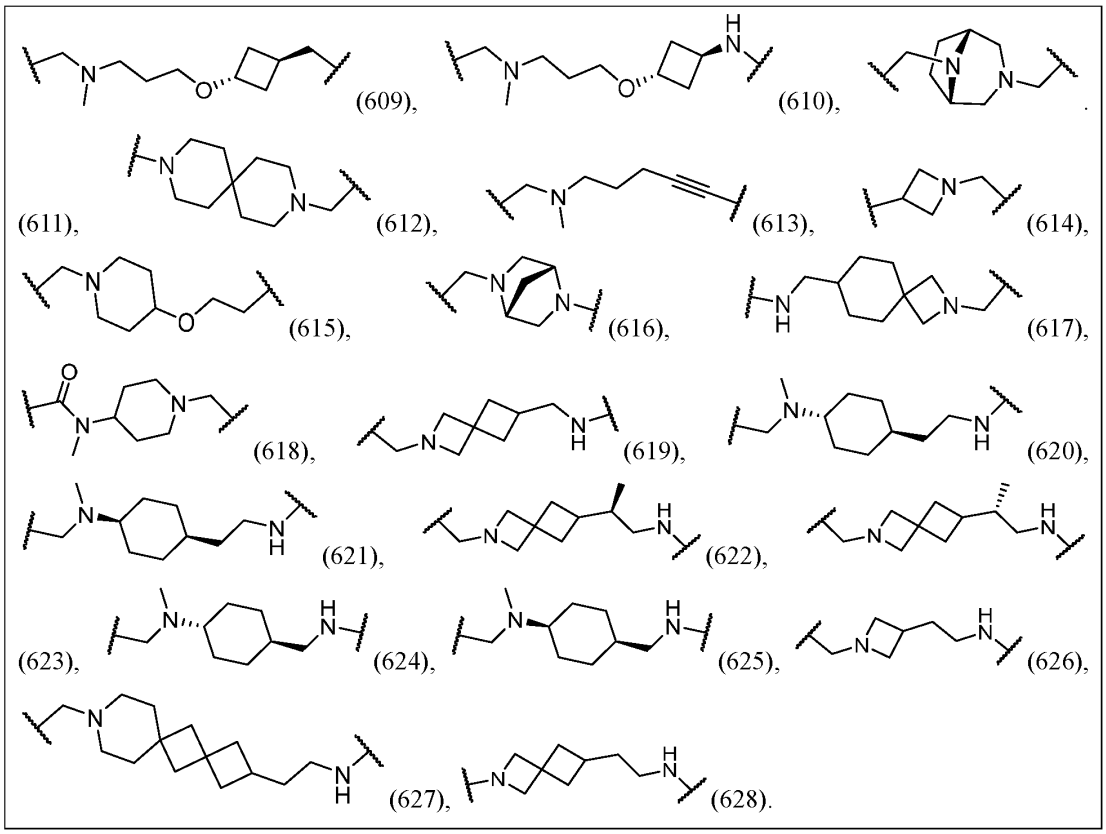

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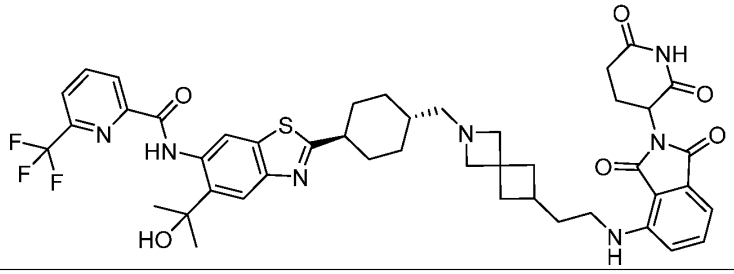
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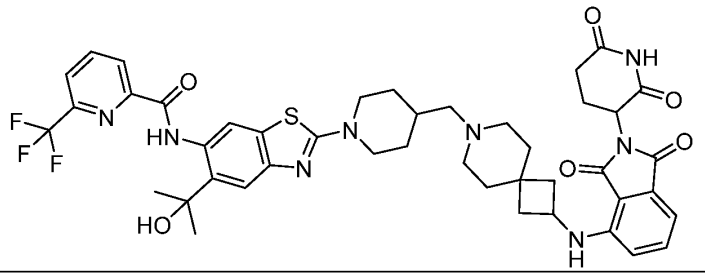
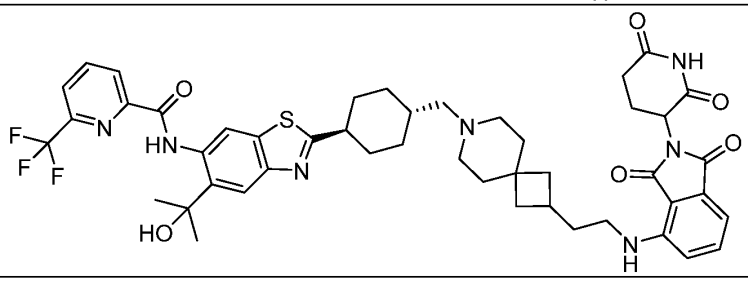
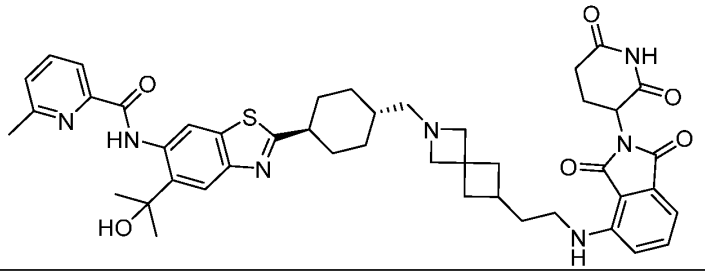
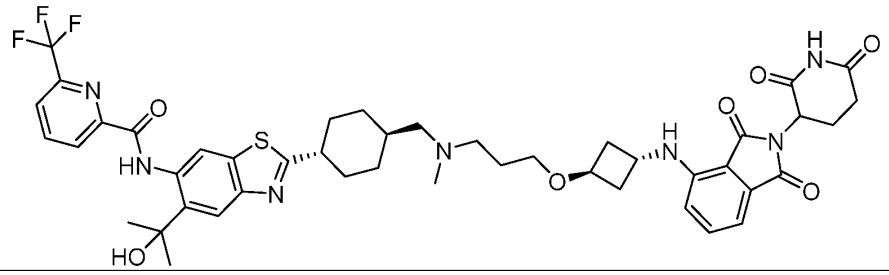
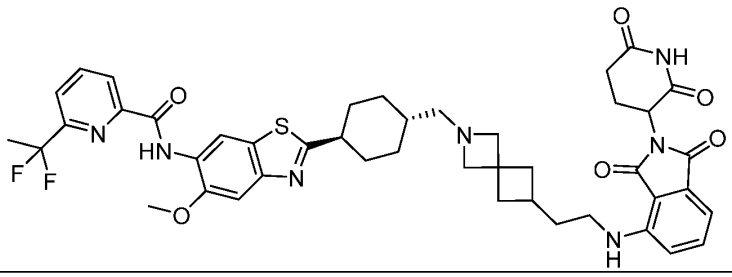


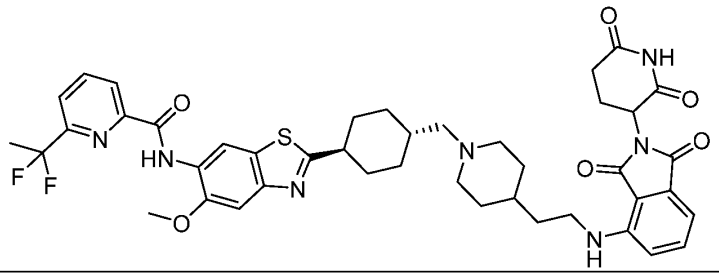
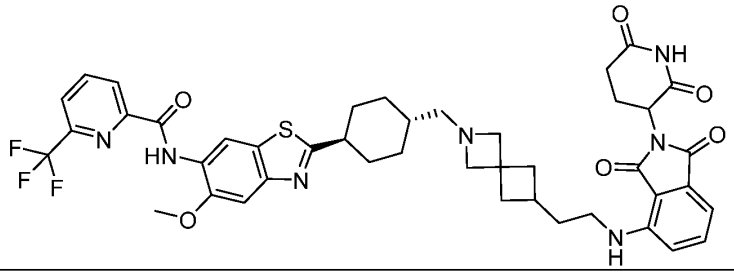
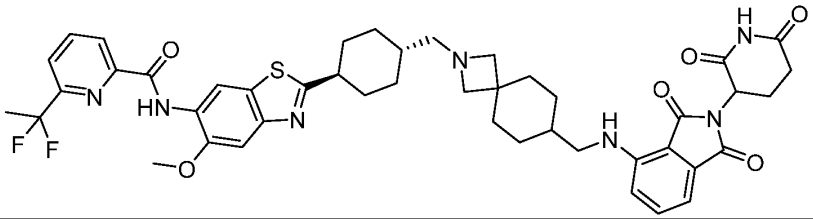
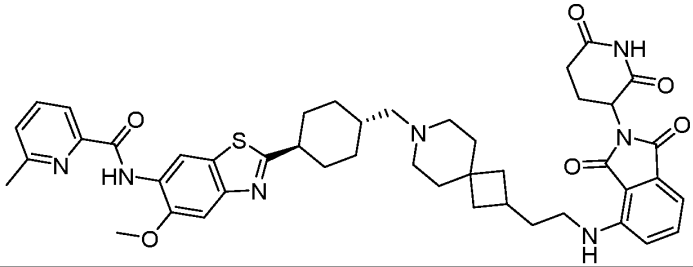
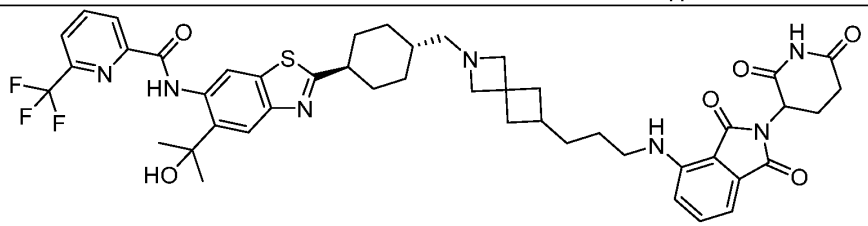
[00207] In some embodiments, the present invention provides a compound having an IRAK binding moiety described and disclosed herein, a LBM set forth in **Table A** above, and a linker set forth in **Table B** above, or a pharmaceutically acceptable salt thereof.

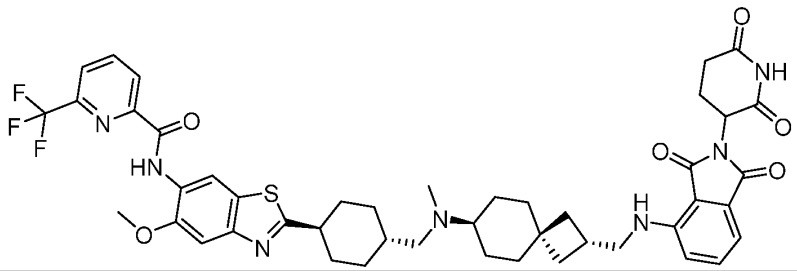
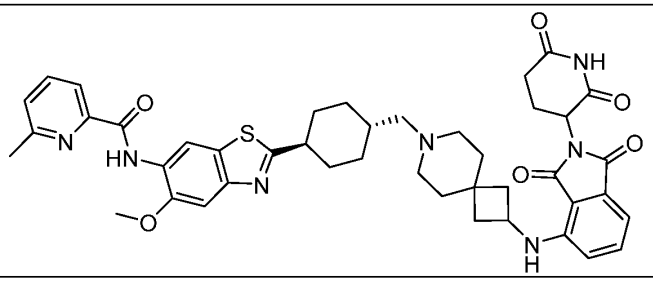
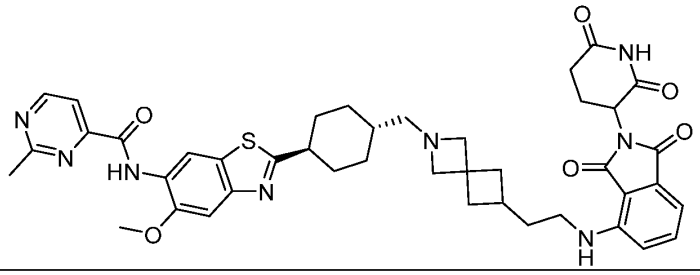
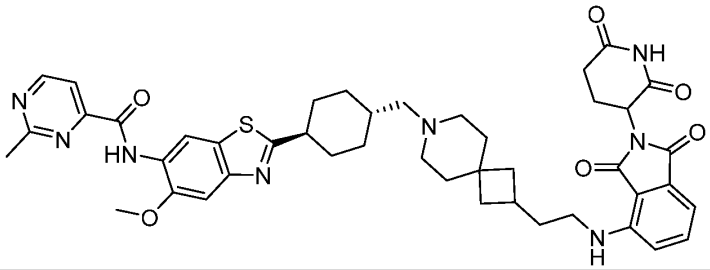
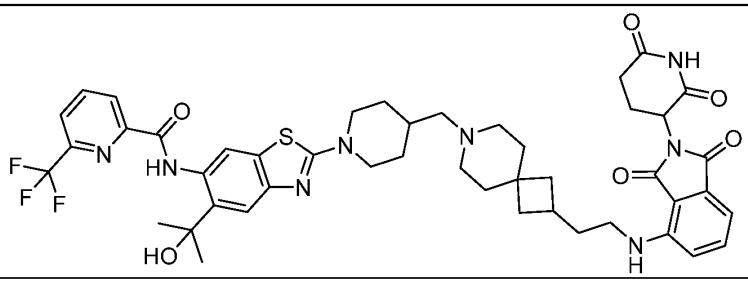
[00208] Exemplary compounds of the invention are set forth in **Table 1**, below.

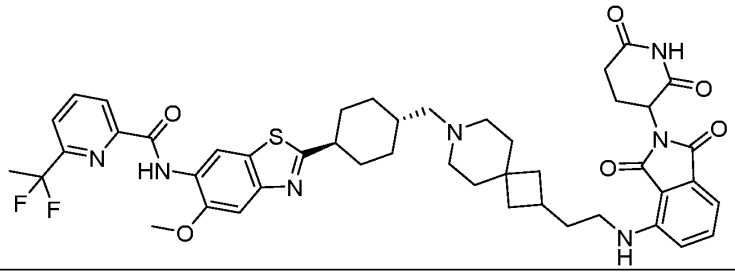
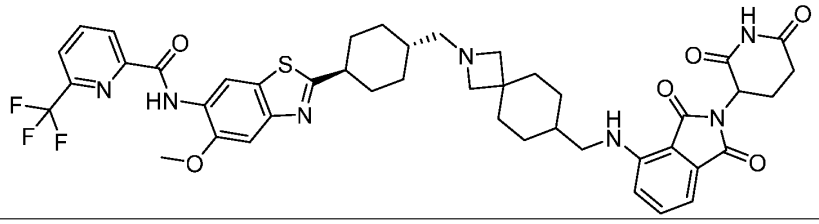
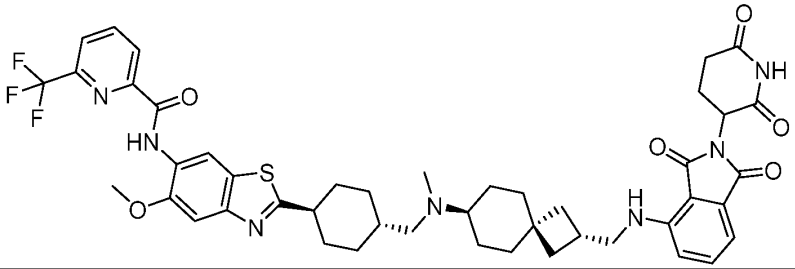
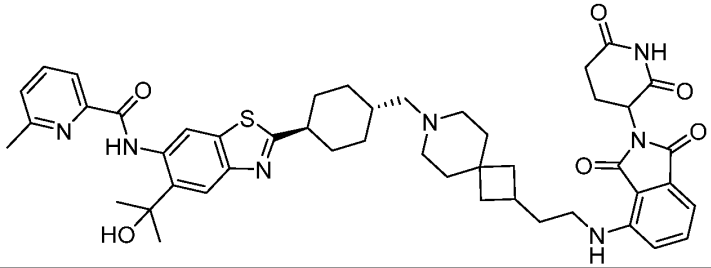
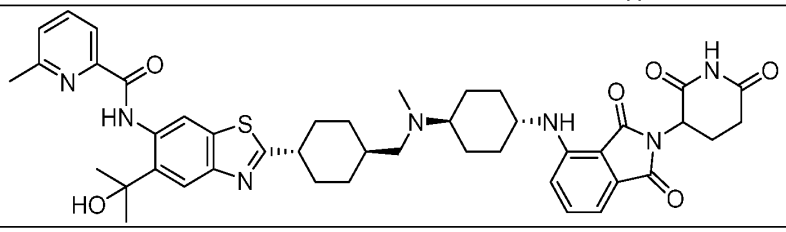
Table 1. Exemplary Compounds

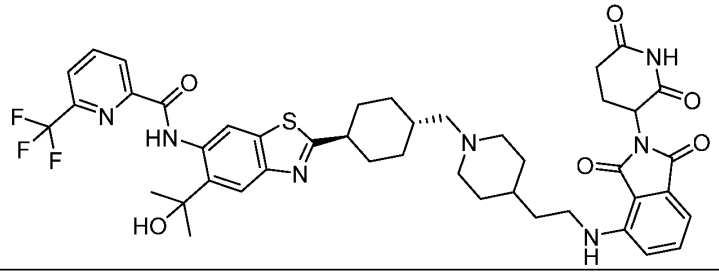
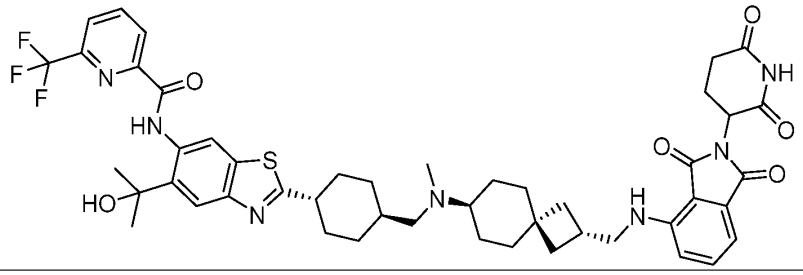
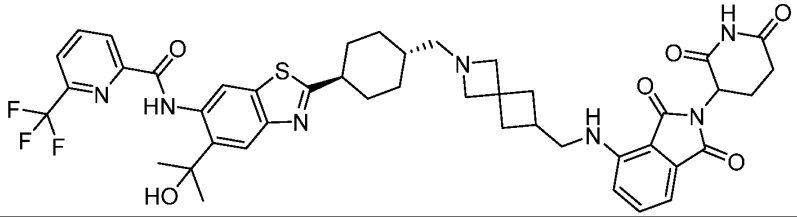
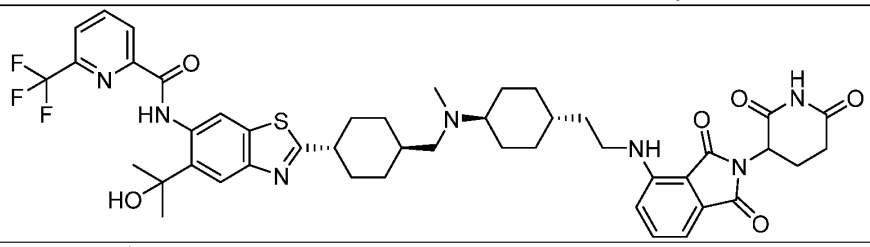
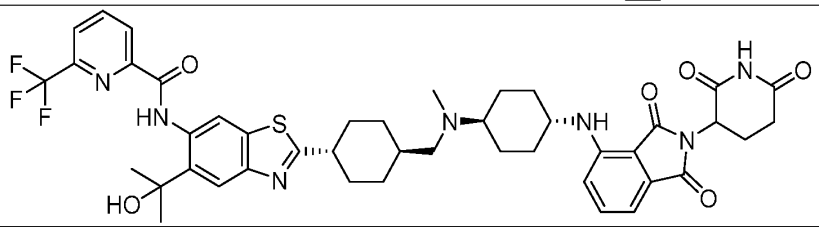
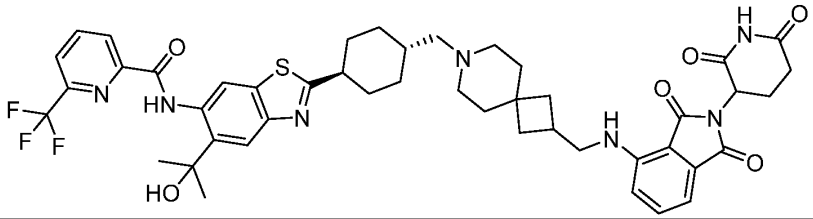
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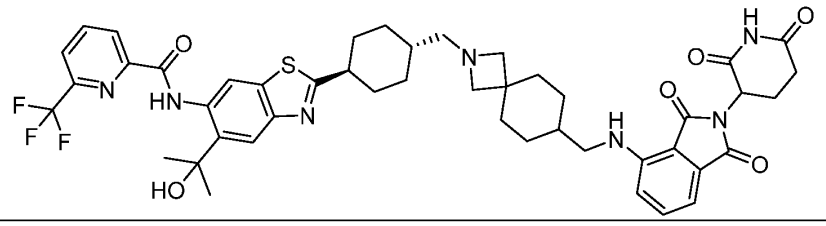
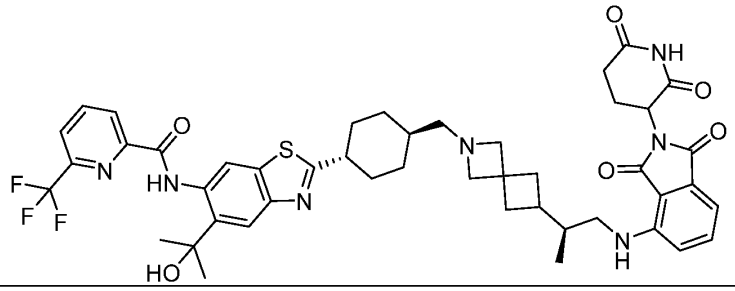
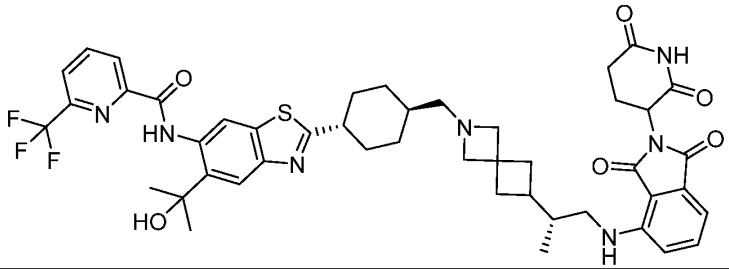
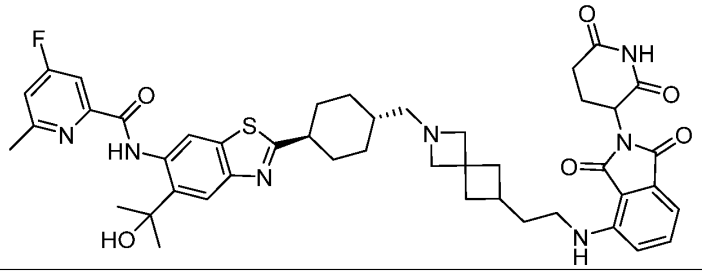
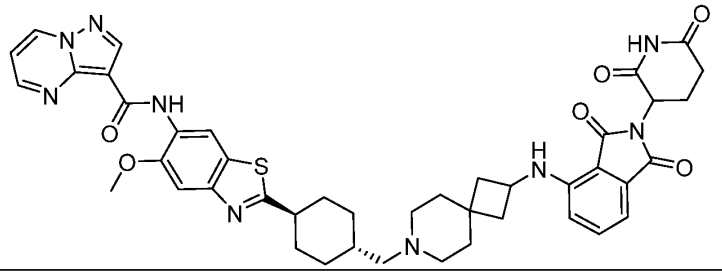
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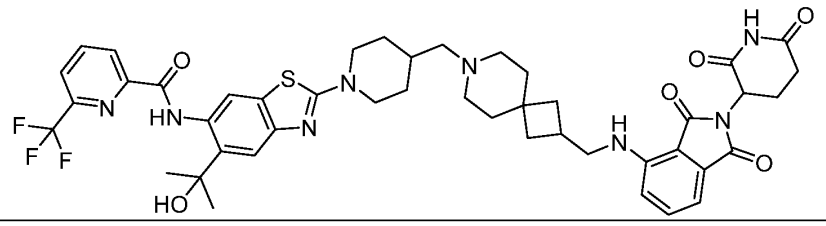
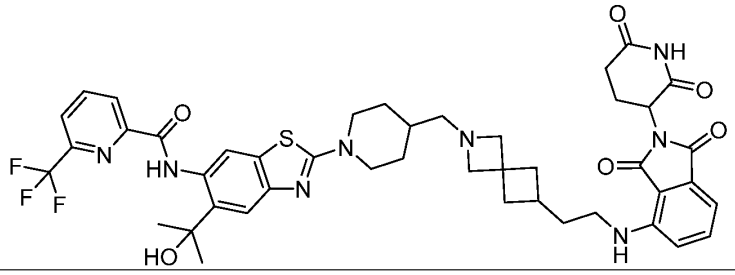
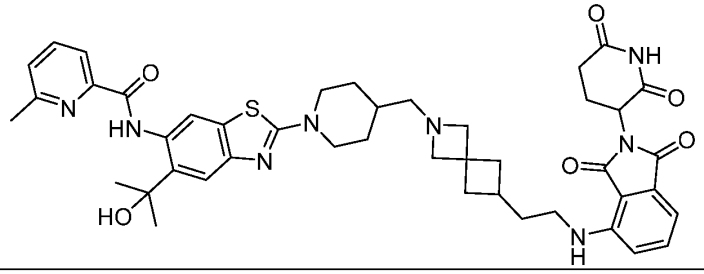
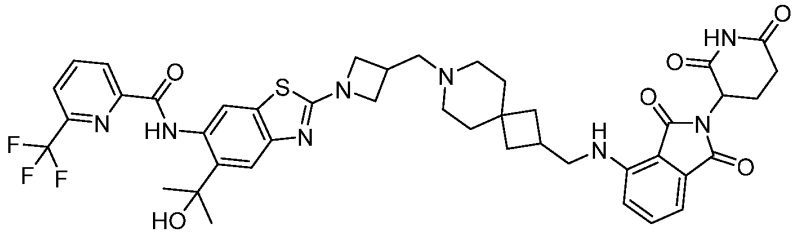
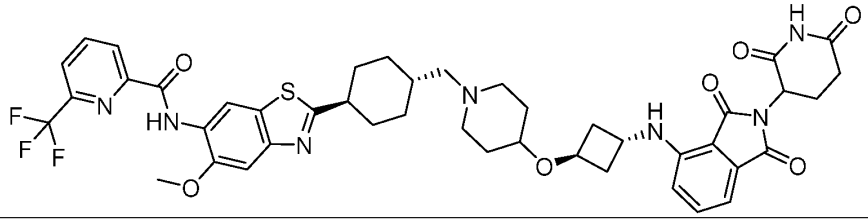
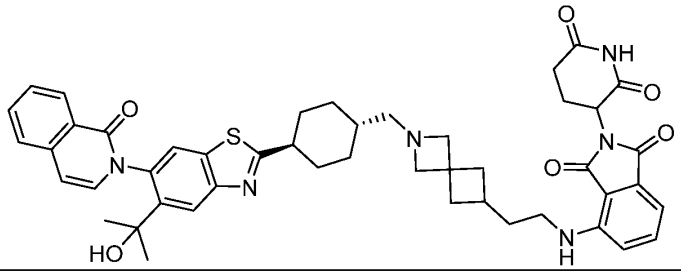
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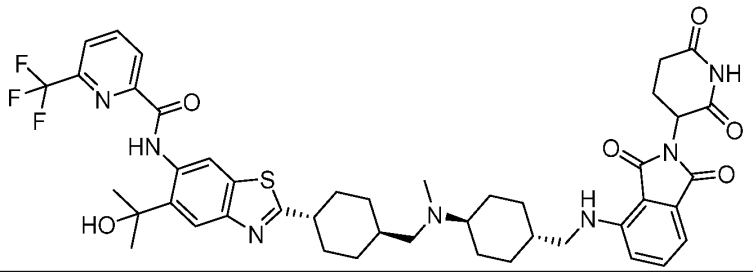
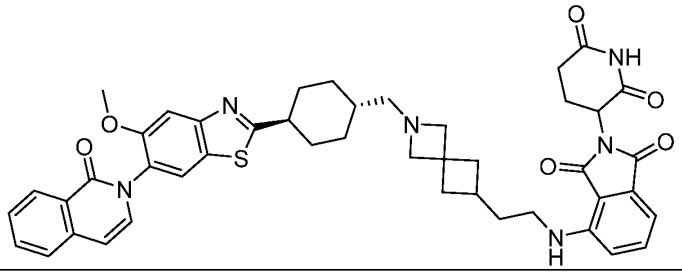
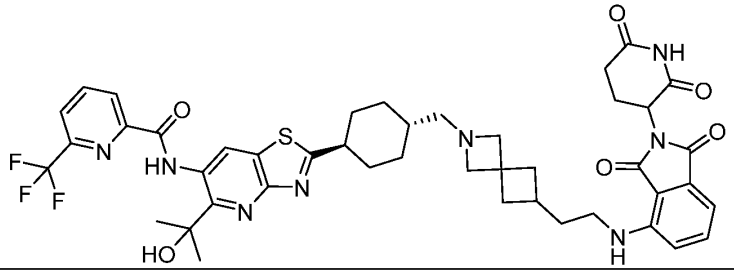
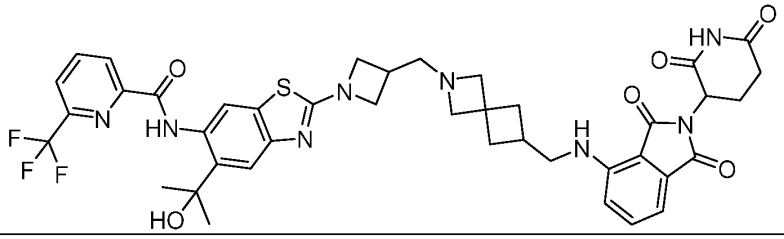
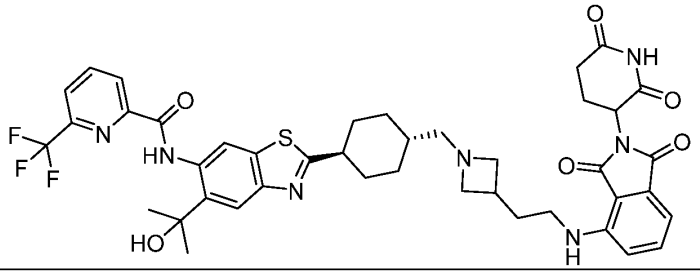
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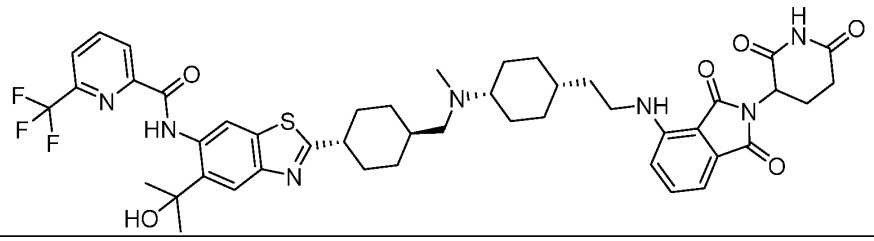
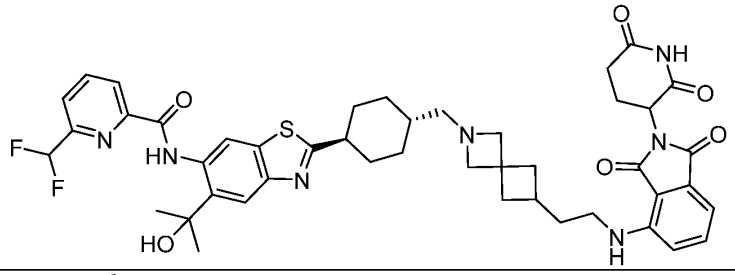
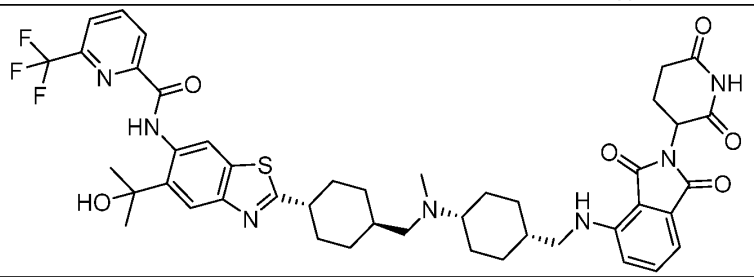
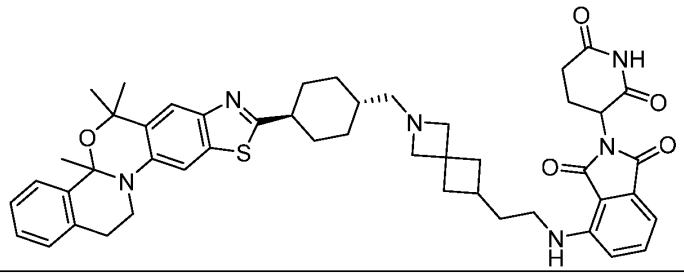
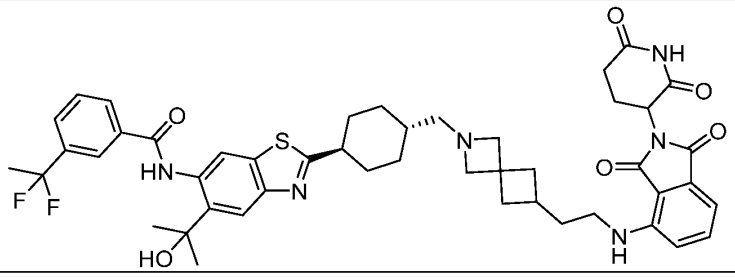
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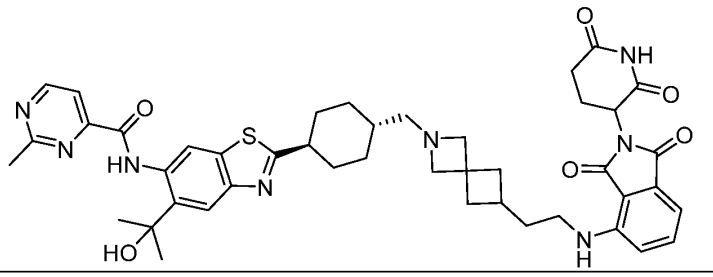
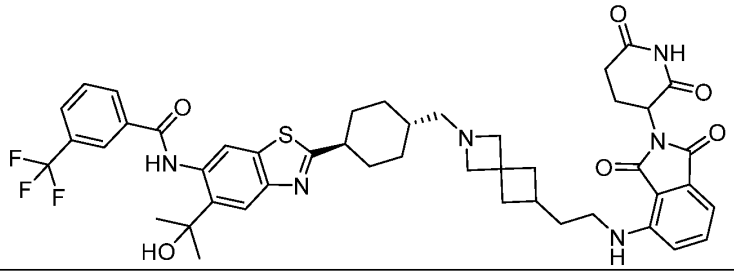
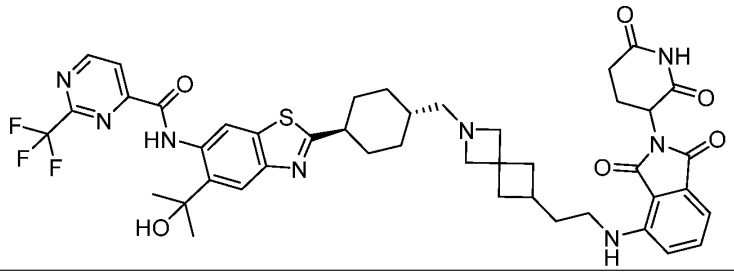
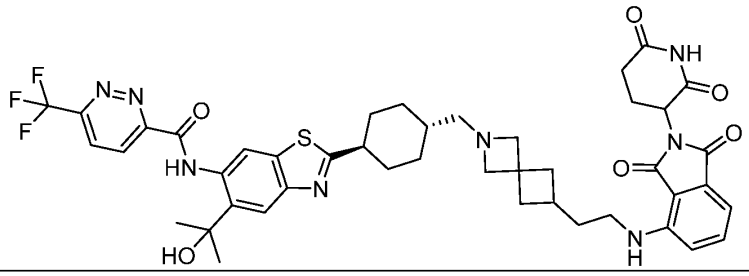
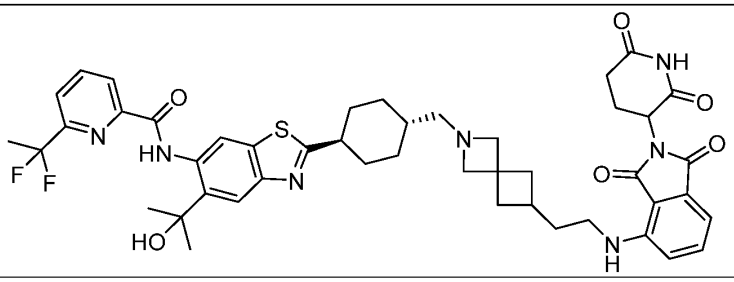
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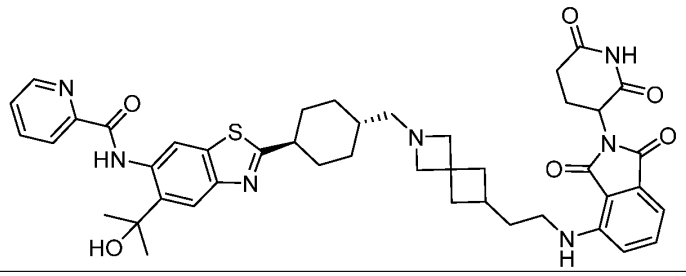
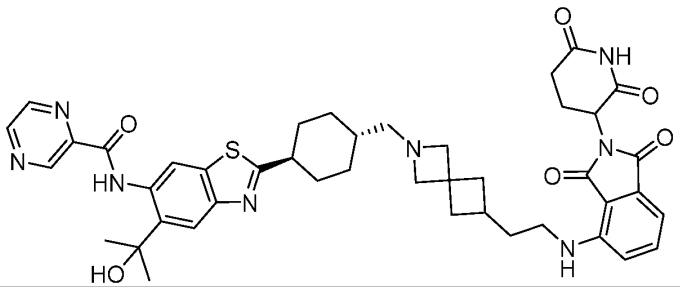
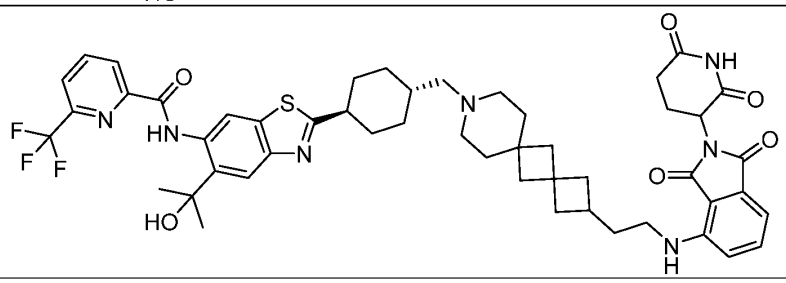
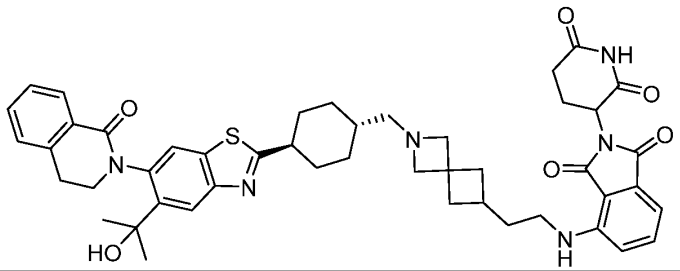
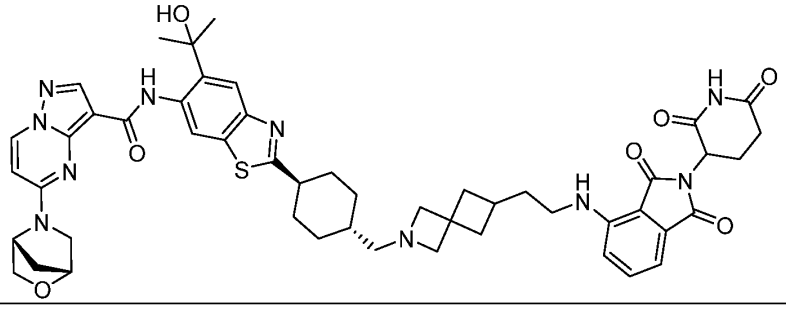
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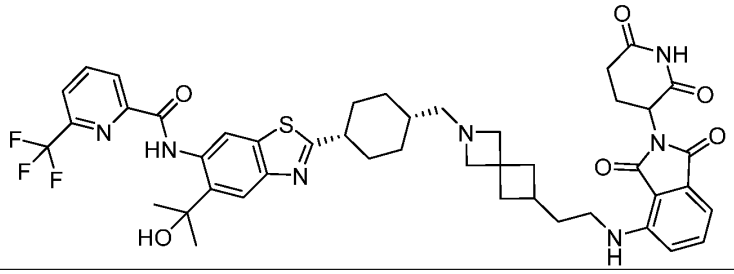
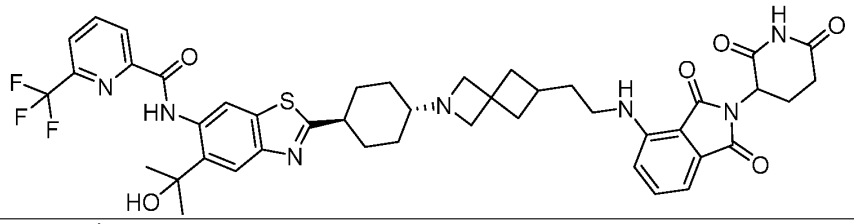
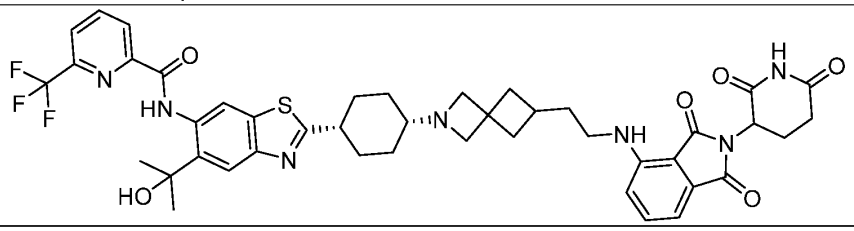
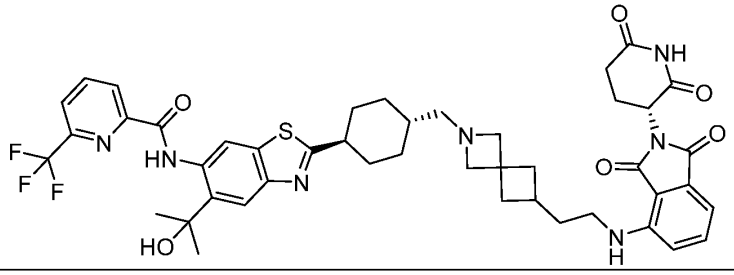
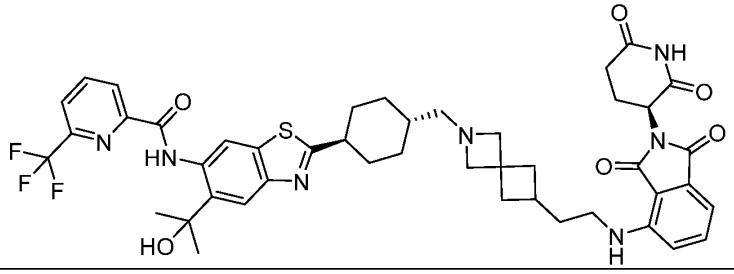
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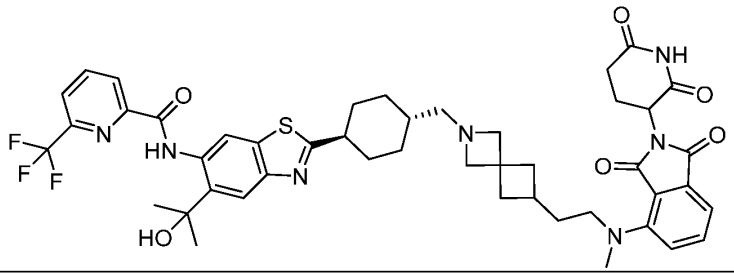
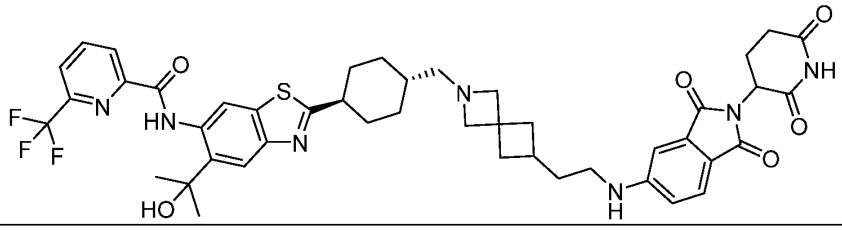
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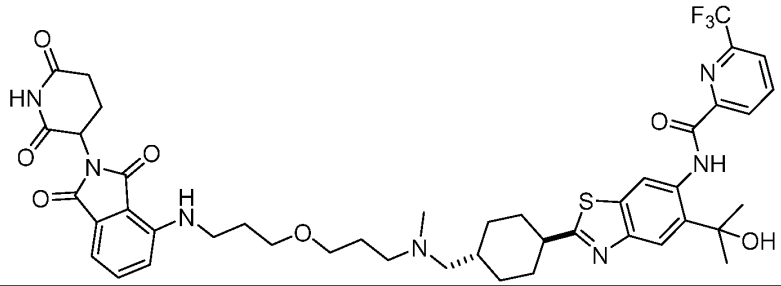
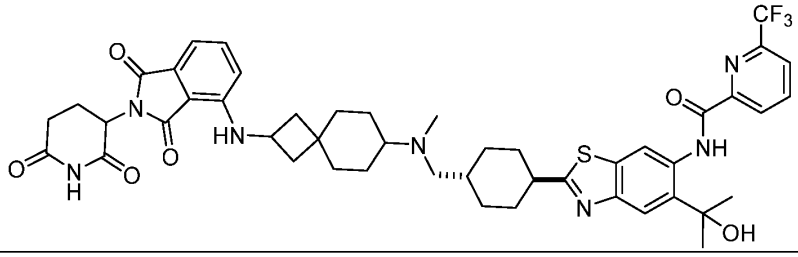
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I-66	

I-67	
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[00209] In some embodiments, the present invention provides a compound as depicted in **Table 1**, above, or a pharmaceutically acceptable salt thereof.

[00210] In some embodiments, the present invention provides a compound of formula **I**, wherein the compound is not any of the compounds depicted in **Table 1A**, below.

Table 1A.

I-#	Structure
I-1	
I-2	

[00211] In some embodiments, the present invention does not provide a compound set forth in **Table 1A**, above, or a pharmaceutically acceptable salt thereof.

4. General Methods of Providing the Present Compounds

[00212] The compounds of this invention may be prepared or isolated in general by synthetic and/or semi-synthetic methods known to those skilled in the art for analogous compounds and by methods described in detail in the Examples, herein.

[00213] In the Schemes below, where a particular protecting group, leaving group, or transformation condition is depicted, one of ordinary skill in the art will appreciate that other protecting groups, leaving groups, and transformation conditions are also suitable and are contemplated. Such groups and transformations are described in detail in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, M. B. Smith and J. March, 5th Edition, John Wiley & Sons, 2001, *Comprehensive Organic Transformations*, R. C. Larock, 2nd Edition, John Wiley & Sons, 1999, and *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of each of which is hereby incorporated herein by reference.

[00214] As used herein, the phrase "oxygen protecting group" includes, for example, carbonyl protecting groups, hydroxyl protecting groups, etc. Hydroxyl protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of each of which is herein incorporated by reference. Examples of suitable hydroxyl protecting groups include, but are not limited to, esters, allyl ethers, ethers, silyl ethers, alkyl ethers, arylalkyl ethers, and alkoxyalkyl ethers. Examples of such esters include formates, acetates, carbonates, and sulfonates. Specific examples include formate, benzoyl formate, chloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate, 4,4-(ethylenedithio)pentanoate, pivaloate (trimethylacetyl), crotonate, 4-methoxy-crotonate, benzoate, p-benylbenzoate, 2,4,6-trimethylbenzoate, carbonates such as methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, vinyl, allyl, and p-nitrobenzyl. Examples of such silyl ethers include trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, and other trialkylsilyl ethers. Alkyl ethers include methyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, trityl, t-butyl, allyl, and allyloxycarbonyl ethers or derivatives. Alkoxyalkyl ethers include acetals such as methoxymethyl, methylthiomethyl, (2-methoxyethoxy)methyl, benzyloxymethyl, beta-(trimethylsilyl)ethoxymethyl, and tetrahydropyranyl ethers. Examples of arylalkyl ethers include benzyl, p-methoxybenzyl (MPM), 3,4-dimethoxybenzyl, O-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, and 2- and 4-picolyl.

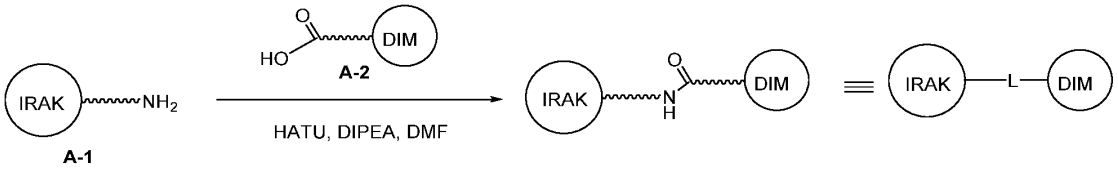
[00215] Amino protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of each of which is herein incorporated by reference. Suitable amino protecting groups

include, but are not limited to, aralkylamines, carbamates, cyclic imides, allyl amines, amides, and the like. Examples of such groups include t-butyloxycarbonyl (BOC), ethyloxycarbonyl, methyloxycarbonyl, trichloroethyloxycarbonyl, allyloxycarbonyl (Alloc), benzyloxocarbonyl (CBZ), allyl, phthalimide, benzyl (Bn), fluorenylmethylcarbonyl (Fmoc), formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, trifluoroacetyl, benzoyl, and the like.

[00216] In the schemes below, where a provided compound is formed having a reactive DIM moiety (e.g., amine, alcohol, etc.), it is not shown but it is generally appreciated and well known by those having ordinary skill in the art that the reactivity of said reactive DIM moiety may be masked by employing a suitable protecting group that can thereafter be removed in situ or during a separate synthetic step.

[00217] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 1 set forth below:

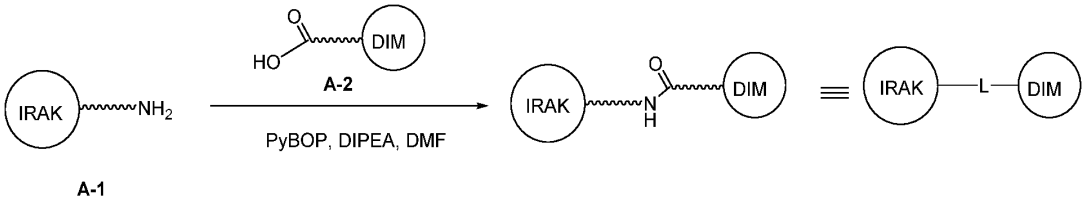
Scheme 1: Synthesis of Compounds of the Invention



[00218] As depicted in Scheme 1, above, amine **A-1** is coupled to acid **A-2** using the coupling agent HATU in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal amino group of **A-1** or the portion of the linker between DIM and the terminal carboxyl group of **A-2**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00219] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 2 set forth below:

Scheme 2: Synthesis of Compounds of the Invention

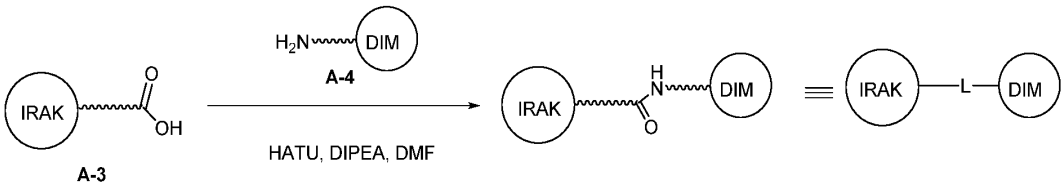


[00220] As depicted in Scheme 2, above, amine **A-1** is coupled to acid **A-2** using the coupling agent PyBOP in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, ~~~, represents the portion of the linker between IRAK

and the terminal amino group of **A-1** or the portion of the linker between DIM and the terminal carboxyl group of **A-2**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00221] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 3 set forth below:

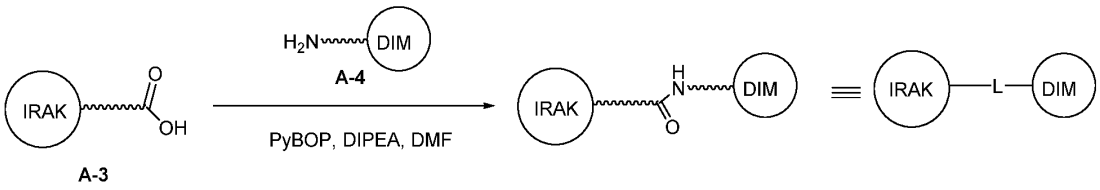
Scheme 3: Synthesis of Compounds of the Invention



[00222] As depicted in Scheme 3, above, acid **A-3** is coupled to amine **A-4** using the coupling agent HATU in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal carboxyl group of **A-3** or the portion of the linker between DIM and the terminal amino group of **A-4**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00223] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 4 set forth below:

Scheme 4: Synthesis of Compounds of the Invention

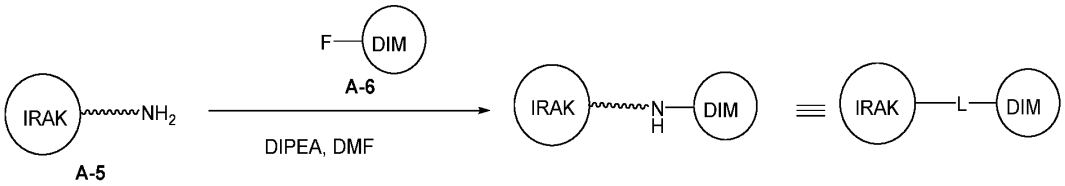


[00224] As depicted in Scheme 4, above, acid **A-3** is coupled to amine **A-4** using the coupling agent PyBOP in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising an amide bond. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal carboxyl group of **A-3** or the portion of the linker between DIM and the terminal amino group of **A-4**, respectively. Additionally, an amide bond can be formed using coupling reagents known in the art such as, but not limited to DCC, DIC, EDC, HBTU, HCTU, PyAOP, PyBrOP, BOP, BOP-Cl, DEPBT, T3P, TATU, TBTU, TNTU, TOTU, TPTU, TSTU, or TDBTU.

[00225] In certain embodiments, compounds of the present invention are generally prepared according

to Scheme 5 set forth below:

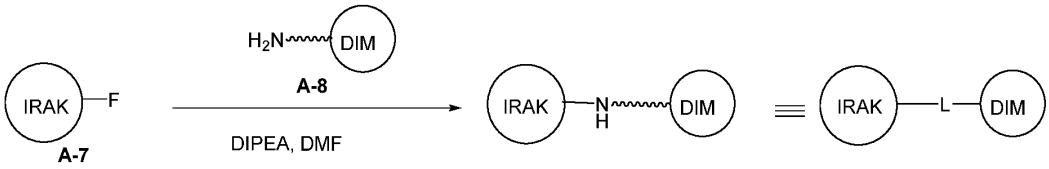
Scheme 5: Synthesis of Compounds of the Invention



[00226] As depicted in Scheme 5, above, an S_NAr displacement of fluoride **A-6** by amine **A-5** is effected in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising a secondary amine. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal amino group of **A-5**.

[00227] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 6 set forth below:

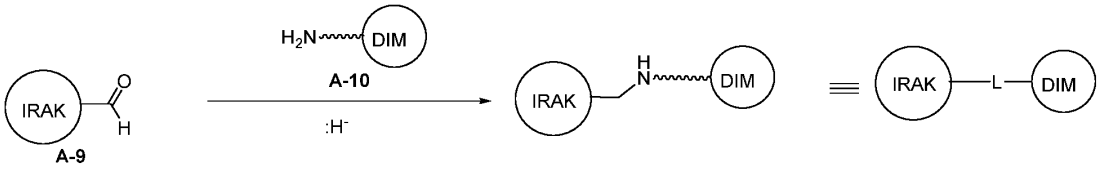
Scheme 6: Synthesis of Compounds of the Invention



[00228] As depicted in Scheme 6, above, an S_NAr displacement of fluoride **A-7** by amine **A-8** is effected in the presence of the base DIPEA in DMF to form a compound of the invention with a linker comprising a secondary amine. The squiggly bond, ~~~, represents the portion of the linker between DIM and the terminal amino group of **A-8**.

[00229] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 7 set forth below:

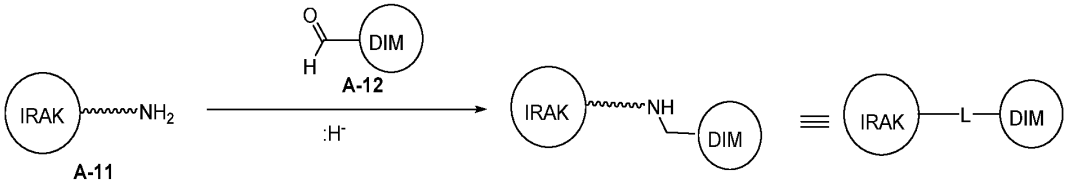
Scheme 7: Synthesis of Compounds of The Invention



[00230] As depicted in Scheme 7, above, reductive alkylation of aldehyde **A-9** by amine **A-10** is effected in the presence of a mild hydride source (*e.g.*, sodium cyanoborohydride or sodium triacetoxyborohydride) to form a provided compound with a linker comprising a secondary amine. The squiggly bond, ~~~, represents the portion of the linker between DIM and the terminal amino group of **A-10**.

[00231] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 8 set forth below:

Scheme 8: Synthesis of Compounds of The Invention



[00232] As depicted in Scheme 8, above, reductive alkylation of aldehyde **A-12** by amine **A-11** is effected in the presence of a mild hydride source (*e.g.*, sodium cyanoborohydride or sodium triacetoxyborohydride) to form a provided compound with a linker comprising a secondary amine. The squiggly bond, ~~~~, represents the portion of the linker between IRAK and the terminal amino group of **A-11**.

[00233] One of skill in the art will appreciate that various functional groups present in compounds of the invention such as aliphatic groups, alcohols, carboxylic acids, esters, amides, aldehydes, halogens and nitriles can be interconverted by techniques well known in the art including, but not limited to reduction, oxidation, esterification, hydrolysis, partial oxidation, partial reduction, halogenation, dehydration, partial hydration, and hydration. See for example, "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entirety of each of which is herein incorporated by reference. Such interconversions may require one or more of the aforementioned techniques, and certain methods for synthesizing compounds of the invention are described below in the Exemplification.

5. Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[00234] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that it is effective to measurably degrade and/or inhibit an IRAK protein kinase, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this invention is such that it is effective to measurably degrade and/or inhibit an IRAK protein kinase, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[00235] The term "patient," as used herein, means an animal, preferably a mammal, and most preferably a human.

[00236] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00237] A "pharmaceutically acceptable derivative" means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily or degratorily active metabolite or residue thereof.

[00238] As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of an IRAK protein kinase, or a mutant thereof.

[00239] As used herein, the term "degratorily active metabolite or residue thereof" means that a metabolite or residue thereof is also a degrader of an IRAK protein kinase, or a mutant thereof.

[00240] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[00241] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of

injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00242] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00243] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00244] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00245] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00246] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl

alcohol and water.

[00247] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00248] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00249] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this invention are administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

[00250] The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the compound can be administered to a patient receiving these compositions.

[00251] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00252] Compounds and compositions described herein are generally useful for the degradation and/or inhibition of kinase activity of one or more enzymes.

[00253] Examples of kinases that are degraded and/or inhibited by the compounds and compositions described herein and against which the methods described herein are useful include those of the interleukin-1 receptor-associated kinase (IRAK) family of kinases, the members of which include IRAK-1, IRAK-2, and IRAK-4, or a mutant thereof. Li et al., "IRAK-4: A novel member of the IRAK family with the

properties of an IRAK-kinase," *PNAS* 2002, 99(8), 5567-5572, Flannery et al., "The interleukin-1 receptor-associated kinases: Critical regulators of innate immune signaling" Biochem Pharm 2010, 80(12), 1981-1991 incorporated by reference in its entirety.

[00254] The activity of a compound utilized in this invention as a degrader and/or inhibitor of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, may be assayed in vitro, in vivo or in a cell line. In vitro assays include assays that determine inhibition of either the phosphorylation activity and/or the subsequent functional consequences, or ATPase activity of activated IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof. Alternate in vitro assays quantitate the ability of the inhibitor to bind to IRAK-1, IRAK-2 and/or IRAK-4. Inhibitor binding may be measured by radiolabeling the inhibitor prior to binding, isolating the inhibitor/IRAK-1, inhibitor/IRAK-2, or inhibitor/IRAK-4 complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with IRAK-1, IRAK-2, and/or IRAK-4 bound to known radioligands. Representative in vitro and in vivo assays useful in assaying an IRAK-4 inhibitor include those described and disclosed in, *e.g.*, Kim et al., "A critical role for IRAK4 kinase activity in Toll-like receptor-mediated innate immunity," *J. Exp. Med.* 2007 204(5), 1025-1036; Lebakken et al., "A Fluorescence Lifetime Based Binding Assay to Characterize Kinase Inhibitors," *J. Biomol. Screen.* 2007, 12(6), 828-841; Maschera et al., "Overexpression of an enzymatically inactive interleukin-1-receptor-associated kinase activates nuclear factor-κB," *Biochem. J.* 1999, 339, 227-231; Song et al., "The kinase activities of interleukin-e receptor associated kinase (IRAK)-1 and 4 are redundant in the control of inflammatory cytokine expression in human cells," *Mol. Immunol.* 2009, 46, 1458-1466, each of, the entirety of each of which is herein incorporated by reference. Detailed conditions for assaying a compound utilized in this invention as a degrader and/or inhibitor of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, are set forth in the Examples below.

[00255] The best characterized member of the IRAK family is the serine/threonine kinase IRAK-4. IRAK-4 is implicated in signaling innate immune responses from Toll-like receptors (TLRs) and Toll/IL-1 receptors (TIRs).

[00256] Innate immunity detects pathogens through the recognition of pathogen-associated molecular patterns by TLRs, when then links to the adaptive immune response. TLRs recognize conserved structures of both microbes and endogenous molecules. TLRs which recognize bacterial and fungal components are located on the cell surface, whereas TLRs which recognize viral or microbial nucleic acids are localized to intracellular membranes such as endosomes and phagosomes. Cell surface TLRs can be targeted by small molecules and antibodies, whereas intracellular TLRs require targeting with oligonucleotides.

[00257] TLRs mediate the innate immune response by upregulating the expression of inflammatory genes in multiple target cells. *See, e.g.*, Sen et al., "Transcriptional signaling by double-stranded RNA: role

of TLR3," *Cytokine & Growth Factor Rev*. 2005, 16, 1-14, incorporated by reference in its entirety. While TLR-mediated inflammatory response is critical for innate immunity and host defense against infections, uncontrolled inflammation is detrimental to the host leading to sepsis and chronic inflammatory diseases, such as chronic arthritis, atherosclerosis, multiple sclerosis, cancers, autoimmune disorders such as rheumatoid arthritis, lupus, asthma, psoriasis, and inflammatory bowel diseases.

[00258] Upon binding of a ligand, most TLRs recruit the adaptor molecule MyD88 through the TIR domain, mediating the MyD88-dependent pathway. MyD88 then recruits IRAK-4, which engages with the nuclear factor-κB (NF-κB), mitogen-activated protein (MAP) kinase and interferon-regulatory factor cascades and leads to the induction of pro-inflammatory cytokines. The activation of NF-κB results in the induction of inflammatory cytokines and chemokines, such as TNF-α, IL-1 α, IL-6 and IL-8. The kinase activity of IRAK-4 has been shown to play a critical role in the TLR-mediated immune and inflammatory responses. IRAK4 is a key mediator of the innate immune response orchestrated by interleukin-1 receptor (IL-1R), interleukin-18 receptor (IL-18R), IL-33 receptor (IL-33R), and Toll-like receptors (TLRs). Inactivation of IRAK-1 and/or IRAK-4 activity has been shown to result in diminished production of cytokines and chemokines in response to stimulation of IL-1 and TLR ligands. *See*, *e.g.*, Picard et al., "Clinical features and outcome of patients with IRAK-4 and MyD88 deficiency," *Medicine (Baltimore)*, 2010, 89(6), 043-25; Li, "IRAK4 in TLR/IL-1R signaling: Possible clinical applications," *Eur. J. Immunology* 2008, 38:614-618; Cohen et al., "Targeting protein kinases for the development of anti-inflammatory drugs," *Curr. Opin. Cell Bio*. 2009, 21:317-324; Flannery et al., "The interleukin-1 receptor-associated kinases: Critical regulators of innate immune signalling," *Biochem. Pharm*. 2010, 80(12), 1981-1991; Gottipati et al., "IRAK1: A critical signaling mediator of innate immunity," *Cellular Signaling* 2008, 20, 269-276; Kim et al., "A critical role for IRAK4 kinase activity in Toll-like receptor-mediated innate immunity," *J. Exp. Med*. 2007 204(5), 1025-1036; Koziczak-Holbro et al., "IRAK-4 Kinase Activity Is Required for Interleukin-1 (IL-1) Receptor- and Toll-like Receptor 7-mediated Signaling and Gene Expression," *J. Biol. Chem*. 2007, 282(18), 13552-13560; Kubo-Murai et al., "IRAK-4-dependent Degradation of IRAK-1 is a Negative Feedback Signal for TLR-mediated NF-κB Activation," *J. Biochem*. 2008, 143, 295-302; Maschera et al., "Overexpression of an enzymatically inactive interleukin-1-receptor-associated kinase activates nuclear factor-κB," *Biochem. J*. 1999, 339, 227-231; Lin et al., "Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR /IL-1R signalling," *Nature* 2010, 465(17), 885-891; Suzuki et al., "IRAK-4 as the central TIR signaling mediator in innate immunity," *TRENDS in Immunol*. 2002, 23(10), 503-506; Suzuki et al., "Severe impairment of interleukin-1 and Toll-like receptor signalling in mice lacking IRAK-4," *Nature* 2002, 416, 750-754; Swantek et al., "IL-1 Receptor-Associated Kinase Modulates Host Responsiveness to Endotoxin," *J. Immunol*. 2000, 164, 4301-4306; Hennessy, E., et al., "Targeting Toll-like receptors: emerging therapeutics?" *Nature Reviews*, vol. 9, pp: 293-307 (2010);

Dinarello, C. "Interleukin-18 and the Pathogenesis of Inflammatory Diseases," *Seminars in Nephrology*, vol. 27, no. 1, pp: 98-114 (2007), each of, the entirety of each of which is herein incorporated by reference. In fact, knockdown mice that express a catalytically inactive mutant IRAK-4 protein are completely resistant to septic shock and show impaired IL-1 activity. Moreover, these mice are resistant to joint and bone inflammation/destruction in an arthritis model, suggesting that IRAK-4 may be targeted to treat chronic inflammation. Further, while IRAK-4 appears to be vital for childhood immunity against some pyogenic bacteria, it has been shown to play a redundant role in protective immunity to most infections in adults, as demonstrated by one study in which patients older than 14 lacking IRAK-4 activity exhibited no invasive infections. Cohen et al., "Targeting protein kinases for the development of anti-inflammatory drugs," *Curr. Opin. Cell Bio*. 2009, 21:317-324; Ku et al., "Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity," *J. Exp. Med*. 2007, 204(10), 2407-2422; Picard et al., "Inherited human IRAK-4 deficiency: an update," *Immunol. Res*. 2007, 38, 347-352; Song et al., "The kinase activities of interleukin-e receptor associated kinase (IRAK)-1 and 4 are redundant in the control of inflammatory cytokine expression in human cells," *Mol. Immunol*. 2009, 46, 1458-1466; Rokosz, L. et al., "Kinase inhibitors as drugs for chronic inflammatory and immunological diseases: progress and challenges," *Expert Opinions on Therapeutic Targets*, 12(7), pp: 883-903 (2008); Gearing, A. "Targeting toll-like receptors for drug development: a summary of commercial approaches," *Immunology and Cell Biology*, 85, pp: 490-494 (2007); Dinarello, C. "IL-1: Discoveries, controversies and future directions," *European Journal of Immunology*, 40, pp: 595-653 (2010), each of, the entirety of each of which is herein incorporated by reference. Because TLR activation triggers IRAK-4 kinase activity, IRAK-4 inhibition presents an attractive target for treating the underlying causes of inflammation in countless diseases.

[00259] Representative IRAK-4 inhibitors include those described and disclosed in *e.g.*, Buckley et al., *Bioorg. Med. Chem. Lett*. 2008, 18, 3211-3214; Buckley et al., *Bioorg. Med. Chem. Lett*. 2008, 18, 3291-3295; Buckley et al., *Bioorg. Med. Chem. Lett*. 2008, 18, 3656-3660; Powers et al., "Discovery and initial SAR of inhibitors of interleukin-1 receptor-associated kinase-4," *Bioorg. Med. Chem. Lett*. 2006, 16, 2842-2845; Wng et al., "IRAK-4 Inhibitors for Inflammation," *Curr. Topics in Med. Chem*. 2009, 9, 724-737, each of, the entirety of each of which is herein incorporated by reference.

[00260] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also

be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[00261] Provided compounds are degraders and/or inhibitors of one of more of IRAK-1, IRAK-2, and/or IRAK-4 and are therefore useful for treating one or more disorders associated with activity of one or more of IRAK-1, IRAK-2, and/or IRAK-4. Thus, in certain embodiments, the present invention provides a method for treating a IRAK-1-mediated, a IRAK-2-mediated, and/or a IRAK-4-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[00262] As used herein, the terms "IRAK-1-mediated", "IRAK-2-mediated", and/or "IRAK-4-mediated" disorders, diseases, and/or conditions as used herein means any disease or other deleterious condition in which one or more of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, are known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which one or more of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, are known to play a role.

[00263] In some embodiments, the present invention provides a method for treating one or more disorders, diseases, and/or conditions wherein the disorder, disease, or condition is a cancer, a neurodegenative disorder, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, conditions associated with organ transplantation, immunodeficiency disorders, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, a cardiovascular disorder, or a CNS disorder.

[00264] Diseases and conditions treatable according to the methods of this invention include, but are not limited to, cancer (*see, e.g.*, Ngo, V. et al., "Oncogenically active *MYD88* mutations in human lymphoma," *Nature*, vol. 000, pp: 1-7 (2010); Lust, J. et al., "Induction of a Chronic Disease State in patients With Smoldering of Indolent Multiple Myeloma by Targeting Interleukin 1ß-Induced Interleukin 6 Production and the Myeloma Proliferative Component," *Mayo Clinic Proceedings*, 84(2), pp: 114-122 (2009)), diabetes, cardiovascular disease, viral disease, autoimmune diseases such as lupus (*see, e.g.*, Dinarello, C. " Interleukin-18 and the Pathogenesis of Inflammatory Diseases," *Seminars in Nephrology*, vol. 27, no. 1, pp: 98-114 (2007); Cohen et al., "Targeting protein kinases for the development of anti-inflammatory drugs," *Curr. Opin. Cell Bio*. 2009, 21:317-324) and rheumatoid arthritis (*see, e.g.*, Geyer, M. et al., "Actual status of antiinterleukin-1 therapies in rheumatic diseases," *Current Opinion in Rheumatology*, 22, pp: 246-251 (2010)), autoinflammatory syndromes (*see, e.g.*, Hoffman, H. et al., "Efficacy and Safety of Rilonacept (Interleukin-1 Trap) in Patients with Cryopyrin-Associated Periodic Syndromes," *Arthritis & Rheumatism*, vol. 58, no. 8, pp: 2443-2452 (2008)), atherosclerosis, psoriasis, allergic disorders, inflammatory bowel disease (*see, e.g.*, Cario, E. "Therapeutic Impact of Toll-like

Receptors on Inflammatory Bowel Diseases: A Multiple-edged Sword," *Inflamm. Bowel Dis.*, 14, pp: 411-421 (2008)), inflammation (*see, e.g.*, Dinarello, C. "Interleukin 1 and interleukin 18 as mediators of inflammation and the aging process, " *The American Journal of Clinical Nutrition*, 83, pp: 447S-455S (2006)), acute and chronic gout and gouty arthritis (*see, e.g.*, Terkeltaub, R. "Update on gout: new therapeutic strategies and options," *Nature*, vol. 6, pp: 30-38 (2010); Weaver, A. "Epidemiology of gout," *Cleveland Clinic Journal of Medicine*, vol. 75, suppl. 5, pp: S9-S12 (2008); Dalbeth, N. et al., "Hyperuricaemia and gout: state of the art and future perspectives," *Annals of Rheumatic Diseases*, 69, pp: 1738-1743 (2010); Martinon, F. et al., "Gout-associated uric acid crystals activate the NALP3 inflammasome," *Nature*, vol. 440, pp: 237-241 (2006); So, A. et al., "A pilot study of IL-1 inhibition by anakinra in acute gout," *Arthritis Research & Therapy*, vol. 9, no. 2, pp: 1-6 (2007); Terkeltaub, R. et al., "The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study," *Annals of Rheumatic Diseases*, 68, pp: 1613-1617 (2009); Torres, R. et al., "Hyperalgesia, synovitis and multiple biomarkers of inflammation are suppressed by interleukin 1 inhibition in a novel animal model of gouty arthritis," *Annals of Rheumatic Diseases*, 68, pp: 1602-1608 (2009)), neurological disorders, metabolic syndrome (*see, e.g.*, Troseid, M. "The role of interleukin-18 in the metabolic syndrome," *Cardiovascular Diabetology*, 9:11, pp:1-8 (2010)), immunodeficiency disorders such as AIDS and HIV (*see, e.g.*, Iannello, A. et al., "Role of Interleukin-18 in the Development and Pathogenesis of AIDS," *AIDS Reviews*, 11, pp: 115-125 (2009)), destructive bone disorders (*see, e.g.*, Hennessy, E., et al., "Targeting Toll-like receptors: emerging therapeutics?" *Nature Reviews*, vol. 9, pp: 293-307 (2010)), osteoarthritis, proliferative disorders, Waldenström's Macroglobulinemia (*see, e.g.*, Treon, et al., "Whole genome sequencing reveals a widely expressed mutation (MYD88 L265P) with oncogenic activity in Waldenström's Macroglobulinemia" 53rd ASH Annual Meeting; Xu, et al., "A somatic variant in MYD88 (L256P) revealed by whole genome sequencing differentiates lymphoplasmacytic lymphoma from marginal zone lymphomas" 53rd ASH Annual Meeting; Yang et al., "Disruption of MYD88 pathway signaling leads to loss of constitutive IRAK1, NK-kB and JAK/STAT signaling and induces apoptosis of cells expressing the MYD88 L265P mutation in Waldenström's Macroglobulinemia" 53rd ASH Annual Meeting; Iriyama et al., "Clinical significance of genetic mutations of CD79B, CARD11, MYD88, and EZH2 genes in diffuse large B-cell lymphoma patients" 53rd ASH Annual Meeting; infectious diseases, conditions associated with cell death, pathologic immune conditions involving T cell activation, and CNS disorders in a patient. In one embodiment, a human patient is treated with a compound of the current invention and a pharmaceutically acceptable carrier, adjuvant, or vehicle, wherein said compound is present in an amount to measurably degrade and/or inhibit IRAK-1 only, IRAK-2-only, IRAK-4-only and/or IRAK1 and IRAK4 kinase activity.

[00265] Compounds of the current invention are useful in the treatment of a proliferative disease

selected from a benign or malignant tumor, solid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastomas, neuroblastomas, multiple myeloma, gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, Hodgkins and Non-Hodgkins, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, an IL-1 driven disorder, an MyD88 driven disorder, Smoldering of indolent multiple myeloma, or hematological malignancies (including leukemia, diffuse large B-cell lymphoma (DLBCL), ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, plasmacytoma, intravascular large B-cell lymphoma, AML, MDS).

[00266] In some embodiments the proliferative disease which can be treated according to the methods of this invention is an MyD88 driven disorder. In some embodiments, the MyD88 driven disorder which can be treated according to the methods of this invention is selected from ABC DLBCL, primary CNS lymphomas, primary extranodal lymphomas, Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma and chronic lymphocytic leukemia.

[00267] In some embodiments the proliferative disease which can be treated according to the methods of this invention is an IL-1 driven disorder. In some embodiments the IL-1 driven disorder is Smoldering of indolent multiple myeloma.

[00268] Compounds according to the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics.

[00269] Compounds according to the invention are useful in the treatment of heteroimmune diseases. Examples of such heteroimmune diseases include, but are not limited to, graft versus host disease,

transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis.

[00270] Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, such as therapy for or intended to restrict or abort symptomatic attack when it occurs, for example antiinflammatory or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome, common to a substantial percentage of asthmatics and characterized by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

[00271] Compounds of the current invention can be used for other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable and include acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, but not limited to, acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

[00272] With regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, compounds of the invention are also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil- related disorders of the airways consequential or concomitant to Loffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma, eosinophilic asthma, eosinophilic COPD, and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

[00273] Compounds of the invention are also useful in the treatment of inflammatory or allergic

conditions of the skin, for example psoriasis, generalized pustular psoriasis (GPP), psoriasis vulgaris, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acne vulgaris, hidradenitis suppurativa, Sweet Syndrome, pyoderma gangrenosum, and other inflammatory or allergic conditions of the skin.

[00274] Compounds of the invention may also be used for the treatment of other diseases or conditions, such as diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, cryopyrin-associated periodic syndrome, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minal change nephropathy), chronic granulomatous disease, endometriosis, leptospiriosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, musclewasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic and non-allergic, mild, moderate, severe, bronchitic, and exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, ocular allergy, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, or Type 2 diabetes, appendicitis, atopic dermatitis, asthma, allergy,

blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, or vulvitis.

[00275] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is an disease of the skin. In some embodiments, the inflammatory disease of the skin is selected from contact dermatitits, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, hidradenitis suppurativa, and other inflammatory or allergic conditions of the skin.

[00276] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is selected from acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic juvenile idiopathic arthritis (SJIA), cryopyrin associated periodic syndrome (CAPS), adult onset Still's disease, macrophage activation syndrome (MAS), primary and secondary hemophagocytic lymphohistiocytosis (HLH), familial mediterranean fever, NLRP12 autoinflammatory syndrome, and osteoarthritis.

[00277] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is a TH17 mediated disease. In some embodiments the TH17 mediated disease is selected from Systemic lupus erythematosus, Multiple sclerosis, psoriasis vulgaris, hidradenitis suppurativa, and inflammatory bowel disease (including Crohn's disease or ulcerative colitis).

[00278] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is selected from Sjogren's syndrome, allergic disorders, osteoarthritis, conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca and vernal conjunctivitis, and diseases affecting the nose such as allergic rhinitis or chronic rhinosinusitis with nasal polyps (CRSwNP).

[00279] Cardiovascular diseases which can be treated according to the methods of this invention include, but are not limited to, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, ischemic stroke, congestive heart failure, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, and deep venous thrombosis.

[00280] In some embodiments, the neurodegenerative disease which can be treated according to the methods of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity, hypoxia, epilepsy, treatment of diabetes, metabolic syndrome, obesity, organ transplantation and graft versus host disease.

[00281] The loss of IRAK4 function results in decreased Aβ levels in an in vivo murine model of Alzheimer's disease and was associated with diminished microgliosis and astrogliosis in aged mice. Analysis of microglia isolated from the adult mouse brain revealed an altered pattern of gene expression associated with changes in microglial phenotype that were associated with expression of IRF transcription factors that govern microglial phenotype. Further, loss of IRAK4 function also promoted amyloid clearance mechanisms, including elevated expression of insulin-degrading enzyme. Finally, blocking IRAK function restored olfactory behavior (Cameron *et al*. "Loss of Interleukin Receptor-Associated Kinase 4 Signaling Suppresses Amyloid Pathology and Alters Microglial Phenotype in a Mouse Model of Alzheimer's Disease" Journal of Neuroscience (2012) 32(43), 15112-15123).

[00282] In some embodiments the invention provides a method of treating, preventing or lessening the severity of Alzheimer's disease comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt or composition thereof.

[00283] In some embodiments the invention provides a method of treating a disease condition commonly occurring in connection with transplantation. In some embodiments, the disease or condition commonly occurring in connection with transplantation is selected from organ transplantation, organ transplant rejection, and graft versus host disease.

[00284] In some embodiments the invention provides a method of treating a metabolic disease. In some embodiments the metabolic disease is selected from Type 1 diabetes, Type 2 diabetes, metabolic syndrome, and obesity.

[00285] In some embodiments the invention provides a method of treating a viral disease. In some embodiments, the viral infection is HIV infection.

[00286] Furthermore, the invention provides the use of a compound according to the definitions herein, or a pharmaceutically acceptable salt, or a hydrate or solvate thereof for the preparation of a medicament for the treatment of a proliferative disease, an inflammatory disease, an obstructive respiratory disease, a cardiovascular disease, a metabolic disease, a neurological disease, a neurodegenerative disease, a viral disease, or a disorder commonly occurring in connection with transplantation.

Multiple Degradation

[00287] In some embodiments, the invention provides compounds that modulate targeted ubiquitination

and degradation of one or more IRAK kinase. In some embodiments, a provided compound modulates targeted ubiquitination and degradation of one or more IRAK kinase and one or more additional protein. In some instances, a provided compound modulates targeted ubiquitination and degradation of IRAK4 and one, two, three, four, or five additional proteins.

[00288] In certain embodiments, the invention provides compounds that are triple degraders. In certain embodiments, the invention provides compounds that combine IRAK kinase degradation with IKZF1 and IKZF3 degradation using IMiD-based IRAK degraders. Some of the most commonly employed E3 ligase ligands are thalidomide and its derivatives, lenalidomide and pomalidomide, commonly referred to as IMiDs (immunomodulatory imide drugs). These agents are small-molecule ligands of cereblon (CRBN) (Ito et al. "Identification of a primary target of thalidomide teratogenicity" Science 2010, 327(5971):1345-1350), a substrate adaptor for the ubiquitously expressed cullin ring ligase 4 (CUL4)-RBX1-DDB1-CRBN (CUL4CRBN) E3 ligase. It has been shown that thalidomide interacts with CRBN to form a novel surface, resulting in interactions with neosubstrates such as Ikaros (IKZF1) and Aiolos (IKZF3) and their ubiquitination and subsequent proteasomal degradation (Krönke *et al.* "Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells" Science 2014, 343(6168):301-305; and Lu *et al.* "The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins" Science, 2014; 343(6168):305-309). This activity alone has potent antitumor effects in some liquid malignancies, and lenalidomide (Revlimid®) is US Food and Drug Administration approved for the treatment of MCL, multiple myeloma, and myelodysplastic syndromes with deletion of chromosome 5q. Lenalidomide is also undergoing late-stage clinical trials for a number of lymphomas, including MCL and the activated B-cell subtype of diffuse large B-cell lymphoma (ABC DLBCL).

[00289] In some instances, degradation of IRAK4 alone is not sufficient to kill the MYD88 L265P mutant DLBCL cell line OCI-LY10 either in vitro or as a flank xenograft in vivo. In some embodiments, IRAK4 binding moieties coupled to non-IMiD CRBN binders mediate effective knockdown of IRAK4 but have little to no effect on the viability of MYD88 mutant ABC-DLBCL cell lines OCI-LY10 and SU-DHL-2 in vitro.

[00290] In some embodiments, a non-IMiD-based degraders effects IRAK degradation in MYD88 mutant ABC DLBCL cell line tumor xenografts but without causing regression. This is consistent with literature demonstrating no effect on growth of OCI-LY10 or other MYD88 mutant lines when the gene encoding IRAK4 is removed at the DNA level using CRISPR/Cas9 editing (Phelan *et al.* "A multiprotein supercomplex controlling oncogenic signaling in lymphoma" Nature, 2018, 7718:387-391).

[00291] It has been shown that activating MYD88 mutations increase production of beta-IFN, a pro-apoptotic cytokine, in ABC-DLBCL cells (Yang *et al.* "Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma" Cancer Cell 2012, 21(6):723-737). The cells are rendered resistant to this

effect by a concomitant MYD88-driven activation of NFkB signaling via IRF4 and SPIB transactivating CARD11 (Yang, Cancer Cell 2012). IMiDs are also known to increase the IFN response in MYD88 mutant ABC-DLBCL to levels sufficient to increase apoptosis (Yang, Cancer Cell 2012; and Hagner *et al.* "CC-122, a pleiotropic pathway modifier, mimics an interferon response and has antitumor activity in DLBCL" Blood 2015, 126:779-789). This effect has been shown to synergize with inhibition of NFkB signaling to further drive DLBCL cell death (Yang, Cancer Cell 2012).

[00292] In some instances, the combination of an IMiD with a small molecule IRAK4 kinase inhibitor shows little to no additive effect on viability of the MYD88 mutant ABC DLBCL cell lines, such as OCI-LY10. In some embodiments, the combination of an IRAK4 inhibitor with IMiD is less active than an all-in-one IMiD-based IRAK4 degrader.

[00293] In certain embodiments, the combination of IRAK kinase degradation with IKZF1 and IKZF3 degradation in an all-in-one IMiD-based IRAK4 degrader shows potent, single agent activity versus MYD88 mutant ABC DLBCL cell lines *in vitro* and OCI-LY10 xenograft *in vivo*. In some embodiments, an all-in-one combination of an IMiD-based CRBN-binder and an IRAK4 binding moiety yields IRAK4 degraders that retain degradation of Ikaros (IKZF1) and other known IMiDs neosubstrates, while more strongly inducing an interferon response compared to pomalidomide alone. In some embodiments, IMiD-based IRAK4 degraders are potent at killing MYD88 mutant ABD-DLBCL cell lines *in vitro*, demonstrating increased activity versus that obtained from combining an IRAK4 inhibitor with IMiDs as single agents.

[00294] In certain embodiments, a provided compound comprising an IMiD-based E3 ligase degrades IRAK4, Ikaros, and Aiolos in MYD88 mutant ABC DLBCL cell line xenografts in vivo, and strongly induces a signature of interferon-driven proteins exemplified by IFIT1 (interferon-inducible transcript 1) and IFIT3 (interferon-inducible transcript 3). In some embodiments, a provided compound comprising an IMiD-based E3 ligase drives regression of tumor xenographs as a single agent.

[00295] In some embodiments, the provided compounds of present invention highlight a synergy obtained by combining IRAK4 degradation with IMiD induction of interferon response to drive single agent anti-tumor activity in MYD88 mutant DLBCL and possibly in other heme malignancies. In certain embodiments, a provided compound comprising an IMiD-based E3 ligase degrade IRAK4, Ikaros, and Aiolos acts synergistically. In some embodiments, a provided compound comprising an IRAK4 binder and an IMiD-based E3 ligase degrades IRAK4, Ikaros, and Aiolos with increased activity in comparison to a provided compound comprising the same IRAK4 binder and a non-IMiD-based E3 ligase and the same IMiD-based E3 ligase as a single agent.

[00296] In some embodiments, the present invention provides a method of treating solid and liquid tumors in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00297] In some embodiments, the present invention provides a method of treating MYD88-mutant Waldenstrom macroglobulinemia in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00298] In some embodiments, the present invention provides a method of treating a AML, or a subset thereof, in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

[00299] In some embodiments, the present invention provides a method of treating NSCLC in a patient in need thereof, comprising administering a compound of the present invention, or a pharmaceutically acceptable salt thereof.

Combination Therapies

[00300] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00301] In certain embodiments, a provided combination, or composition thereof, is administered in combination with another therapeutic agent.

[00302] In some embodiments, the present invention provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof and co-administering simultaneously or sequentially an effective amount of one or more additional therapeutic agents, such as those described herein. In some embodiments, the method includes co-administering one additional therapeutic agent. In some embodiments, the method includes co-administering two additional therapeutic agents. In some embodiments, the combination of the disclosed compound and the additional therapeutic agent or agents acts synergistically.

[00303] Examples of agents the combinations of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Excelon®; treatments for HIV such as ritonavir; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive

agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents that prolong or improve pharmacokinetics such as cytochrome P450 inhibitors (i.e., inhibitors of metabolic breakdown) and CYP3A4 inhibitors (e.g., ketokenozole and ritonavir), and agents for treating immunodeficiency disorders such as gamma globulin.

[00304] In certain embodiments, combination therapies of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with a monoclonal antibody or an siRNA therapeutic.

[00305] Those additional agents may be administered separately from a provided combination therapy, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[00306] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a combination of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form.

[00307] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00308] One or more other therapeutic agent may be administered separately from a compound or composition of the invention, as part of a multiple dosage regimen. Alternatively, one or more other therapeutic agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as a multiple dosage regime, one or more other therapeutic agent and a compound or composition of the invention may be administered simultaneously, sequentially or within a period of time from one another, for example within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 18, 20, 21, 22, 23, or 24 hours from one another. In some embodiments, one or more other

therapeutic agent and a compound or composition of the invention are administered as a multiple dosage regimen within greater than 24 hours apart.

[00309] In one embodiment, the present invention provides a composition comprising a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents. The therapeutic agent may be administered together with a provided compound or a pharmaceutically acceptable salt thereof, or may be administered prior to or following administration of a provided compound or a pharmaceutically acceptable salt thereof. Suitable therapeutic agents are described in further detail below. In certain embodiments, a provided compound or a pharmaceutically acceptable salt thereof may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours before the therapeutic agent. In other embodiments, a provided compound or a pharmaceutically acceptable salt thereof may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours following the therapeutic agent.

[00310] In another embodiment, the present invention provides a method of treating an inflammatory disease, disorder or condition by administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents. Such additional therapeutic agents may be small molecules or recombinant biologic agents and include, for example, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, colchicine (Colcrys®), corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, probenecid, allopurinol, febuxostat (Uloric®), sulfasalazine (Azulfidine®), antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), methotrexate (Rheumatrex®), gold salts such as gold thioglucose (Solganal®), gold thiomalate (Myochrysine®) and auranofin (Ridaura®), D-penicillamine (Depen® or Cuprimine®), azathioprine (Imuran®), cyclophosphamide (Cytoxan®), chlorambucil (Leukeran®), cyclosporine (Sandimmune®), leflunomide (Arava®) and "anti-TNF" agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol (Cimzia®) and adalimumab (Humira®), "anti-IL-1" agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), canakinumab (Ilaris®), anti-Jak inhibitors such as tofacitinib, antibodies such as rituximab (Rituxan®), "anti-T-cell" agents such as abatacept (Orencia®), "anti-IL-6" agents such as tocilizumab (Actemra®), diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®), monoclonal antibodies such as tanezumab, anticoagulants such as heparin (Calcinparine® or Liquaemin®) and warfarin (Coumadin®), antidiarrheals such as diphenoxylate (Lomotil®) and loperamide (Imodium®), bile acid binding agents such as cholestyramine,

alosetron (Lotronex®), lubiprostone (Amitiza®), laxatives such as Milk of Magnesia, polyethylene glycol (MiraLax®), Dulcolax®, Correctol® and Senokot®, anticholinergics or antispasmodics such as dicyclomine (Bentyl®), Singulair®, beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), inhaled corticosteroids such as beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmacort®), mometasone (Asthmanex®), budesonide (Pulmocort®), and flunisolide (Aerobid®), Afviar®, Symbicort®, Dulera®, cromolyn sodium (Intal®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyl®, Theo-24®) and aminophylline, IgE antibodies such as omalizumab (Xolair®), nucleoside reverse transcriptase inhibitors such as zidovudine (Retrovir®), abacavir (Ziagen®), abacavir/lamivudine (Epzicom®), abacavir/lamivudine/zidovudine (Trizivir®), didanosine (Videx®), emtricitabine (Emtriva®), lamivudine (Epivir®), lamivudine/zidovudine (Combivir®), stavudine (Zerit®), and zalcitabine (Hivid®), non-nucleoside reverse transcriptase inhibitors such as delavirdine (Rescriptor®), efavirenz (Sustiva®), nevairapine (Viramune®) and etravirine (Intelence®), nucleotide reverse transcriptase inhibitors such as tenofovir (Viread®), protease inhibitors such as amprenavir (Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Lexiva®), indinavir (Crixivan®), lopinavir and ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Fortovase® or Invirase®), and tipranavir (Aptivus®), entry inhibitors such as enfuvirtide (Fuzeon®) and maraviroc (Selzentry®), integrase inhibitors such as raltegravir (Isentress®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), bortezomib (Velcade®), and dexamethasone (Decadron ®) in combination with lenalidomide (Revlimid ®), or any combination(s) thereof.

[00311] In another embodiment, the present invention provides a method of treating gout comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, colchicine (Colcrys®), corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, probenecid, allopurinol and febuxostat (Uloric®).

[00312] In another embodiment, the present invention provides a method of treating rheumatoid arthritis comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, sulfasalazine (Azulfidine®), antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine

(Aralen®), methotrexate (Rheumatrex®), gold salts such as gold thioglucose (Solganal®), gold thiomalate (Myochrysine®) and auranofin (Ridaura®), D-penicillamine (Depen® or Cuprimine®), azathioprine (Imuran®), cyclophosphamide (Cytoxan®), chlorambucil (Leukeran®), cyclosporine (Sandimmune®), leflunomide (Arava®) and "anti-TNF" agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol (Cimzia®) and adalimumab (Humira®), "anti-IL-1" agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), antibodies such as rituximab (Rituxan®), "anti-T-cell" agents such as abatacept (Orencia®) and "anti-IL-6" agents such as tocilizumab (Actemra®).

[00313] In some embodiments, the present invention provides a method of treating osteoarthritis comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®) and monoclonal antibodies such as tanezumab.

[00314] In some embodiments, the present invention provides a method of treating lupus comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), cyclophosphamide (Cytoxan®), methotrexate (Rheumatrex®), azathioprine (Imuran®) and anticoagulants such as heparin (Calcinparine® or Liquaemin®) and warfarin (Coumadin®).

[00315] In some embodiments, the present invention provides a method of treating inflammatory bowel disease comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from mesalamine (Asacol®) sulfasalazine (Azulfidine®), antidiarrheals such as diphenoxylate (Lomotil®) and loperamide (Imodium®), bile acid binding agents such as cholestyramine, alosetron (Lotronex®), lubiprostone (Amitiza®), laxatives such as Milk of Magnesia, polyethylene glycol (MiraLax®), Dulcolax®, Correctol® and Senokot® and anticholinergics or antispasmodics such as dicyclomine (Bentyl®), anti-TNF therapies, steroids, and antibiotics such as Flagyl or ciprofloxacin.

[00316] In some embodiments, the present invention provides a method of treating asthma comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from anti-IL-33 antibodies such as REGN3500 (SAR440340) or CNTO 7160, Singulair®, beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®),

terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), inhaled corticosteroids such as prednisone, prednisolone, beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmacort®), mometasone (Asthmanex®), budesonide (Pulmocort®), flunisolide (Aerobid®), Afviar®, Symbicort®, and Dulera®, cromolyn sodium (Intal®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyl®, Theo-24®) and aminophylline, and IgE antibodies such as omalizumab (Xolair®).

[00317] In some embodiments, the present invention provides a method of treating COPD comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyl®, Theo-24®) and aminophylline, inhaled corticosteroids such as prednisone, prednisolone, beclomethasone dipropionate (Beclovent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmacort®), mometasone (Asthmanex®), budesonide (Pulmocort®), flunisolide (Aerobid®), Afviar®, Symbicort®, and Dulera®, In some embodiments, the present invention provides a method of treating eosinophilic COPD comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from an anti-IL-33 antibody such as REGN3500 (SAR440340) or CNTO 7160. In some embodiments, the present invention provides a method of treating eosinophilic asthma comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from an anti-IL-33 antibody such as REGN3500 (SAR440340) or CNTO 7160.

[00318] In some embodiments, the present invention provides a method of treating HIV comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from nucleoside reverse transcriptase inhibitors such as zidovudine (Retrovir®), abacavir (Ziagen®), abacavir/lamivudine (Epzicom®), abacavir/lamivudine/zidovudine (Trizivir®), didanosine (Videx®), emtricitabine (Emtriva®), lamivudine (Epivir®), lamivudine/zidovudine (Combivir®), stavudine (Zerit®), and zalcitabine (Hivid®), non-nucleoside reverse transcriptase inhibitors such as delavirdine (Rescriptor®), efavirenz (Sustiva®), nevairapine (Viramune®) and etravirine (Intelence®), nucleotide reverse transcriptase inhibitors such as tenofovir (Viread®), protease inhibitors such as amprenavir (Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Lexiva®), indinavir (Crixivan®), lopinavir and ritonavir (Kaletra®),

nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Fortovase® or Invirase®), and tipranavir (Aptivus®), entry inhibitors such as enfuvirtide (Fuzeon®) and maraviroc (Selzentry®), integrase inhibitors such as raltegravir (Isentress®), and combinations thereof.

[00319] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, a SYK inhibitor, and combinations thereof.

[00320] In another embodiment, the present invention provides a method of treating a solid tumor comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, a SYK inhibitor, and combinations thereof.

[00321] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a Hedgehog (Hh) signaling pathway inhibitor. In some embodiments, the hematological malignancy is DLBCL (Ramirez *et al* "Defining causative factors contributing in the activation of hedgehog signaling in diffuse large B-cell lymphoma" Leuk. Res. (2012), published online July 17, and incorporated herein by reference in its entirety).

[00322] In another embodiment, the present invention provides a method of treating diffuse large B-cell lymphoma (DLBCL) comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, and combinations thereof.

[00323] In some embodiments, the present invention provides a method of treating DLBCL comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a CHOP (cyclophosphamide, Hydrodaunorubicin®, Oncovin®, and prednisone or prednisolone) or R-CHOP (rituximab, cyclophosphamide, Hydrodaunorubicin®, Oncovin®, and prednisone or prednisolone) chemotherapy regimen.

[00324] In some embodiments, the present invention provides a method of treating DLBCL comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a rituximab/bendamustine chemotherapy regimen.

[00325] In some embodiments, the present invention provides a method of treating DLBCL comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a BTK inhibitor (e.g., ibrutinib).

[00326] In some embodiments, the present invention provides a method of treating DLBCL comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and an anti-CD20 antibody (e.g., rituximab).

[00327] In some embodiments, the present invention provides a method of treating DLBCL comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and an anti-CD79B ADC (e.g., polatuzumab).

[00328] In some embodiments, the present invention provides a method of treating DLBCL comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a BCL2 inhibitor (e.g., venetoclax).

[00329] In some embodiments, the present invention provides a method of treating DLBCL comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and lenalidomide or pomalidomide

[00330] In some embodiments, the present invention provides a method of treating DLBCL comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a PI3K inhibitor (e.g., umbralisib).

[00331] In some embodiments, the present invention provides a method of treating a T-cell disease or deficiency describing herein comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a PI3K inhibitor (e.g., umbralisib).

[00332] In some embodiments, the present invention provides a method of treating DLBCL comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a protesome inhibitor (e.g., bortezomib)

[00333] In some embodiments, the present invention provides a method of treating a T-cell disease or deficiency describing herein comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a protesome inhibitor (e.g., bortezomib).

[00334] In another embodiment, the present invention provides a method of treating multiple myeloma comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from bortezomib (Velcade®), and dexamethasone (Decadron®), a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, a SYK inhibitor in combination with lenalidomide (Revlimid®).

[00335] In another embodiment, the present invention provides a method of treating Waldenström's macroglobulinemia comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from chlorambucil (Leukeran®), cyclophosphamide (Cytoxan®, Neosar®), fludarabine (Fludara®), cladribine (Leustatin®), rituximab (Rituxan®), a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, and a SYK inhibitor.

[00336] In some embodiments, one or more other therapeutic agent is an antagonist of the hedgehog pathway. Approved hedgehog pathway inhibitors which may be used in the present invention include sonidegib (Odomzo®, Sun Pharmaceuticals); and vismodegib (Erivedge®, Genentech), both for treatment of basal cell carcinoma.

[00337] In some embodiments, one or more other therapeutic agent is a Poly ADP ribose polymerase (PARP) inhibitor. In some embodiments, a PARP inhibitor is selected from olaparib (Lynparza®, AstraZeneca); rucaparib (Rubraca®, Clovis Oncology); niraparib (Zejula®, Tesaro); talazoparib (MDV3800/BMN 673/LT00673, Medivation/Pfizer/Biomarin); veliparib (ABT-888, AbbVie); and BGB-290 (BeiGene, Inc.).

[00338] In some embodiments, one or more other therapeutic agent is a histone deacetylase (HDAC) inhibitor. In some embodiments, an HDAC inhibitor is selected from vorinostat (Zolinza®, Merck); romidepsin (Istodax®, Celgene); panobinostat (Farydak®, Novartis); belinostat (Beleodaq®, Spectrum Pharmaceuticals); entinostat (SNDX-275, Syndax Pharmaceuticals) (NCT00866333); and chidamide (Epidaza®, HBI-8000, Chipscreen Biosciences, China).

[00339] In some embodiments, one or more other therapeutic agent is a CDK inhibitor, such as a CDK4/CDK6 inhibitor. In some embodiments, a CDK 4/6 inhibitor is selected from palbociclib (Ibrance®, Pfizer); ribociclib (Kisqali®, Novartis); abemaciclib (Ly2835219, Eli Lilly); and trilaciclib (G1T28, G1 Therapeutics).

[00340] In some embodiments, one or more other therapeutic agent is a folic acid inhibitor. Approved folic acid inhibitors useful in the present invention include pemetrexed (Alimta®, Eli Lilly).

[00341] In some embodiments, one or more other therapeutic agent is a CC chemokine receptor 4 (CCR4) inhibitor. CCR4 inhibitors being studied that may be useful in the present invention include mogamulizumab (Poteligeo®, Kyowa Hakko Kirin, Japan).

[00342] In some embodiments, one or more other therapeutic agent is an isocitrate dehydrogenase (IDH) inhibitor. IDH inhibitors being studied which may be used in the present invention include AG120 (Celgene; NCT02677922); AG221 (Celgene, NCT02677922; NCT02577406); BAY1436032 (Bayer, NCT02746081); IDH305 (Novartis, NCT02987010).

[00343] In some embodiments, one or more other therapeutic agent is an arginase inhibitor. Arginase inhibitors being studied which may be used in the present invention include AEB1102 (pegylated recombinant arginase, Aeglea Biotherapeutics), which is being studied in Phase 1 clinical trials for acute myeloid leukemia and myelodysplastic syndrome (NCT02732184) and solid tumors (NCT02561234); and CB-1158 (Calithera Biosciences).

[00344] In some embodiments, one or more other therapeutic agent is a glutaminase inhibitor. Glutaminase inhibitors being studied which may be used in the present invention include CB-839 (Calithera Biosciences).

[00345] In some embodiments, one or more other therapeutic agent is an antibody that binds to tumor antigens, that is, proteins expressed on the cell surface of tumor cells. Approved antibodies that bind to tumor antigens which may be used in the present invention include rituximab (Rituxan®, Genentech/BiogenIdec); ofatumumab (anti-CD20, Arzerra®, GlaxoSmithKline); obinutuzumab (anti-CD20, Gazyva®, Genentech), ibritumomab (anti-CD20 and Yttrium-90, Zevalin®, Spectrum Pharmaceuticals); daratumumab (anti-CD38, Darzalex®, Janssen Biotech), dinutuximab (anti-glycolipid GD2, Unituxin®, United Therapeutics); trastuzumab (anti-HER2, Herceptin®, Genentech); ado-trastuzumab emtansine (anti-HER2, fused to emtansine, Kadcyla®, Genentech); and pertuzumab (anti-HER2, Perjeta®, Genentech); and brentuximab vedotin (anti-CD30-drug conjugate, Adcetris®, Seattle Genetics).

[00346] In some embodiments, one or more other therapeutic agent is a topoisomerase inhibitor. Approved topoisomerase inhibitors useful in the present invention include irinotecan (Onivyde®, Merrimack Pharmaceuticals); topotecan (Hycamtin®, GlaxoSmithKline). Topoisomerase inhibitors being studied which may be used in the present invention include pixantrone (Pixuvri®, CTI Biopharma).

[00347] In some embodiments, one or more other therapeutic agent is an inhibitor of anti-apoptotic proteins, such as BCL-2. Approved anti-apoptotics which may be used in the present invention include venetoclax (Venclexta®, AbbVie/Genentech); and blinatumomab (Blincyto®, Amgen). Other therapeutic agents targeting apoptotic proteins which have undergone clinical testing and may be used in the present invention include navitoclax (ABT-263, Abbott), a BCL-2 inhibitor (NCT02079740).

[00348] In some embodiments, one or more other therapeutic agent is an androgen receptor inhibitor. Approved androgen receptor inhibitors useful in the present invention include enzalutamide (Xtandi®, Astellas/Medivation); approved inhibitors of androgen synthesis include abiraterone (Zytiga®, Centocor/Ortho); approved antagonist of gonadotropin-releasing hormone (GnRH) receptor (degaralix, Firmagon®, Ferring Pharmaceuticals).

[00349] In some embodiments, one or more other therapeutic agent is a selective estrogen receptor modulator (SERM), which interferes with the synthesis or activity of estrogens. Approved SERMs useful in the present invention include raloxifene (Evista®, Eli Lilly).

[00350] In some embodiments, one or more other therapeutic agent is an inhibitor of bone resorption. An approved therapeutic which inhibits bone resorption is Denosumab (Xgeva®, Amgen), an antibody that binds to RANKL, prevents binding to its receptor RANK, found on the surface of osteoclasts, their precursors, and osteoclast-like giant cells, which mediates bone pathology in solid tumors with osseous metastases. Other approved therapeutics that inhibit bone resorption include bisphosphonates, such as zoledronic acid (Zometa®, Novartis).

[00351] In some embodiments, one or more other therapeutic agent is an inhibitor of interaction between the two primary p53 suppressor proteins, MDMX and MDM2. Inhibitors of p53 suppression proteins being studied which may be used in the present invention include ALRN-6924 (Aileron), a stapled peptide that equipotently binds to and disrupts the interaction of MDMX and MDM2 with p53. ALRN-6924 is currently being evaluated in clinical trials for the treatment of AML, advanced myelodysplastic syndrome (MDS) and peripheral T-cell lymphoma (PTCL) (NCT02909972; NCT02264613).

[00352] In some embodiments, one or more other therapeutic agent is an inhibitor of transforming growth factor-beta (TGF-beta or TGFß). Inhibitors of TGF-beta proteins being studied which may be used in the present invention include NIS793 (Novartis), an anti-TGF-beta antibody being tested in the clinic for treatment of various cancers, including breast, lung, hepatocellular, colorectal, pancreatic, prostate and renal cancer (NCT 02947165). In some embodiments, the inhibitor of TGF-beta proteins is fresolimumab (GC1008; Sanofi-Genzyme), which is being studied for melanoma (NCT00923169); renal cell carcinoma (NCT00356460); and non-small cell lung cancer (NCT02581787). Additionally, in some embodiments, the additional therapeutic agent is a TGF-beta trap, such as described in Connolly et al. (2012) Int'l J. Biological Sciences 8:964-978. One therapeutic compound currently in clinical trials for treatment of solid tumors is M7824 (Merck KgaA - formerly MSB0011459X), which is a bispecific, anti-PD-L1/TGFß trap compound (NCT02699515); and (NCT02517398). M7824 is comprised of a fully human IgG1 antibody against PD-L1 fused to the extracellular domain of human TGF-beta receptor II, which functions as a TGFß "trap."

[00353] In some embodiments, one or more other therapeutic agent is selected from glembatumumab vedotin-monomethyl auristatin E (MMAE) (Celldex), an anti-glycoprotein NMB (gpNMB) antibody (CR011) linked to the cytotoxic MMAE. gpNMB is a protein overexpressed by multiple tumor types associated with cancer cells' ability to metastasize.

[00354] In some embodiments, one or more other therapeutic agent is an antiproliferative compound. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens;

topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; matrix metalloproteinase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (Temodal®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array BioPharma, AZd_6244 from AstraZeneca, PD181461 from Pfizer and leucovorin.

[00355] In some embodiments, the present invention provides a method of treating Alzheimer's disease comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from donepezil (Aricept®), rivastigmine (Excelon®), galantamine (Razadyne®), tacrine (Cognex®), and memantine (Namenda®).

[00356] In some embodiments, one or more other therapeutic agent is a taxane compound, which causes disruption of microtubules, which are essential for cell division. In some embodiments, a taxane compound is selected from paclitaxel (Taxol®, Bristol-Myers Squibb), docetaxel (Taxotere®, Sanofi-Aventis; Docefrez®, Sun Pharmaceutical), albumin-bound paclitaxel (Abraxane®; Abraxis/Celgene), cabazitaxel (Jevtana®, Sanofi-Aventis), and SID530 (SK Chemicals, Co.) (NCT00931008).

[00357] In some embodiments, one or more other therapeutic agent is a nucleoside inhibitor, or a therapeutic agent that interferes with normal DNA synthesis, protein synthesis, cell replication, or will otherwise inhibit rapidly proliferating cells.

[00358] In some embodiments, a nucleoside inhibitor is selected from trabectedin (guanidine alkylating agent, Yondelis®, Janssen Oncology), mechlorethamine (alkylating agent, Valchlor®, Aktelion Pharmaceuticals); vincristine (Oncovin®, Eli Lilly; Vincasar®, Teva Pharmaceuticals; Marqibo®, Talon Therapeutics); temozolomide (prodrug to alkylating agent 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC) Temodar®, Merck); cytarabine injection (ara-C, antimetabolic cytidine analog, Pfizer); lomustine (alkylating agent, CeeNU®, Bristol-Myers Squibb; Gleostine®, NextSource Biotechnology); azacitidine (pyrimidine nucleoside analog of cytidine, Vidaza®, Celgene); omacetaxine

mepesuccinate (cephalotaxine ester) (protein synthesis inhibitor, Synribo®; Teva Pharmaceuticals); asparaginase *Erwinia chrysanthemi* (enzyme for depletion of asparagine, Elspar®, Lundbeck; Erwinaze®, EUSA Pharma); eribulin mesylate (microtubule inhibitor, tubulin-based antimitotic, Halaven®, Eisai); cabazitaxel (microtubule inhibitor, tubulin-based antimitotic, Jevtana®, Sanofi-Aventis); capacetrine (thymidylate synthase inhibitor, Xeloda®, Genentech); bendamustine (bifunctional mechlorethamine derivative, believed to form interstrand DNA cross-links, Treanda®, Cephalon/Teva); ixabepilone (semi-synthetic analog of epothilone B, microtubule inhibitor, tubulin-based antimitotic, Ixempra®, Bristol-Myers Squibb); nelarabine (prodrug of deoxyguanosine analog, nucleoside metabolic inhibitor, Arranon®, Novartis); clorafabine (prodrug of ribonucleotide reductase inhibitor, competitive inhibitor of deoxycytidine, Clolar®, Sanofi-Aventis); and trifluridine and tipiracil (thymidine-based nucleoside analog and thymidine phosphorylase inhibitor, Lonsurf®, Taiho Oncology).

[00359] In some embodiments, one or more other therapeutic agent is a kinase inhibitor or VEGF-R antagonist. Approved VEGF inhibitors and kinase inhibitors useful in the present invention include: bevacizumab (Avastin®, Genentech/Roche) an anti-VEGF monoclonal antibody; ramucirumab (Cyramza®, Eli Lilly), an anti-VEGFR-2 antibody and ziv-aflibercept, also known as VEGF Trap (Zaltrap®; Regeneron/Sanofi). VEGFR inhibitors, such as regorafenib (Stivarga®, Bayer); vandetanib (Caprelsa®, AstraZeneca); axitinib (Inlyta®, Pfizer); and lenvatinib (Lenvima®, Eisai); Raf inhibitors, such as sorafenib (Nexavar®, Bayer AG and Onyx); dabrafenib (Tafinlar®, Novartis); and vemurafenib (Zelboraf®, Genentech/Roche); MEK inhibitors, such as cobimetanib (Cotellic®, Exelexis/Genentech/Roche); trametinib (Mekinist®, Novartis); Bcr-Abl tyrosine kinase inhibitors, such as imatinib (Gleevec®, Novartis); nilotinib (Tasigna®, Novartis); dasatinib (Sprycel®, BristolMyersSquibb); bosutinib (Bosulif®, Pfizer); and ponatinib (Inclusig®, Ariad Pharmaceuticals); Her2 and EGFR inhibitors, such as gefitinib (Iressa®, AstraZeneca); erlotinib (Tarceeva®, Genentech/Roche/Astellas); lapatinib (Tykerb®, Novartis); afatinib (Gilotrif®, Boehringer Ingelheim); osimertinib (targeting activated EGFR, Tagrisso®, AstraZeneca); and brigatinib (Alunbrig®, Ariad Pharmaceuticals); c-Met and VEGFR2 inhibitors, such as cabozanitib (Cometriq®, Exelexis); and multikinase inhibitors, such as sunitinib (Sutent®, Pfizer); pazopanib (Votrient®, Novartis); ALK inhibitors, such as crizotinib (Xalkori®, Pfizer); ceritinib (Zykadia®, Novartis); and alectinib (Alecenza®, Genentech/Roche); Bruton's tyrosine kinase inhibitors, such as ibrutinib (Imbruvica®, Pharmacyclics/Janssen); and Flt3 receptor inhibitors, such as midostaurin (Rydapt®, Novartis).

[00360] Other kinase inhibitors and VEGF-R antagonists that are in development and may be used in the present invention include tivozanib (Aveo Pharmaceuticals); vatalanib (Bayer/Novartis); lucitanib (Clovis Oncology); dovitinib (TKI258, Novartis); Chiauanib (Chipscreen Biosciences); CEP-11981 (Cephalon); linifanib (Abbott Laboratories); neratinib (HKI-272, Puma Biotechnology); radotinib

(Supect®, IY5511, Il-Yang Pharmaceuticals, S. Korea); ruxolitinib (Jakafi®, Incyte Corporation); PTC299 (PTC Therapeutics); CP-547,632 (Pfizer); foretinib (Exelexis, GlaxoSmithKline); quizartinib (Daiichi Sankyo) and motesanib (Amgen/Takeda).

[00361] In another embodiment, the present invention provides a method of treating organ transplant rejection or graft vs. host disease comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from a steroid, cyclosporin, FK506, rapamycin, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a TYK2 inhibitor, a PI3K inhibitor, and a SYK inhibitor.

[00362] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a BTK inhibitor, wherein the disease is selected from inflammatory bowel disease, arthritis, systemic lupus erythematosus (SLE), vasculitis, idiopathic thrombocytopenic purpura (ITP), rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease, autoimmune thyroiditis, Sjogren's syndrome, multiple sclerosis, systemic sclerosis, Lyme neuroborreliosis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylosis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, autoimmune gastritis, pernicious anemia, celiac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behcet's disease, chronic fatigue, dysautonomia, membranous glomerulonephropathy, endometriosis, interstitial cystitis, pemphigus vulgaris, bullous pemphigoid, neuromyotonia, scleroderma, vulvodynia, a hyperproliferative disease, rejection of transplanted organs or tissues, Acquired Immunodeficiency Syndrome (AIDS, also known as HIV), type 1 diabetes, graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis, asthma, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis,

prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, or vulvitis, B-cell proliferative disorder, e.g., diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, multiple myeloma (also known as plasma cell myeloma), non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, or lymphomatoid granulomatosis, breast cancer, prostate cancer, or cancer of the mast cells (e.g., mastocytoma, mast cell leukemia, mast cell sarcoma, systemic mastocytosis), bone cancer, colorectal cancer, pancreatic cancer, diseases of the bone and joints including, without limitation, rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome, systemic sclerosis, osteoporosis, bone cancer, bone metastasis, a thromboembolic disorder, (e.g., myocardial infarct, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, deep venous thrombosis), inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholocystitus, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), autoimmune alopecia, pernicious anemia, glomerulonephritis, dermatomyositis, multiple sclerosis, scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, Alzheimer's disease, diabetes, septic shock, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituitarism, Guillain-Barre syndrome, Behcet's disease, scleraderma, mycosis fungoides, acute inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease.

[00363] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a PI3K inhibitor, wherein the disease is selected from a cancer,

a neurodegenative disorder, an angiogenic disorder, a viral disease, an autoimmune disease, an inflammatory disorder, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), liver disease, pathologic immune conditions involving T cell activation, a cardiovascular disorder, and a CNS disorder.

[00364] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and a PI3K inhibitor, wherein the disease is selected from benign or malignant tumor, carcinoma or solid tumor of the brain, kidney (e.g., renal cell carcinoma (RCC)), liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, endometrium, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastomas, neuroblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma or a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, (including, for example, non-Hodgkin's Lymphoma (NHL) and Hodgkin's lymphoma (also termed Hodgkin's or Hodgkin's disease)), a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, or a leukemia, diseases include Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome, or diseases in which the PI3K/PKB pathway is aberrantly activated, asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection, acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy, bronchitis of whatever type or genesis including, but not limited to, acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis, pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, Loffler's syndrome, eosinophilic, pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis,

contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minal change nephropathy, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, ischemic stroke and congestive heart failure, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and cerebral ischemia, and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity and hypoxia.

[00365] In some embodiments, one or more other therapeutic agent is a phosphatidylinositol 3 kinase (PI3K) inhibitor. In some embodiments, a PI3K inhibitor is selected from idelalisib (Zydelig®, Gilead), alpelisib (BYL719, Novartis), taselisib (GDC-0032, Genentech/Roche); pictilisib (GDC-0941, Genentech/Roche); copanlisib (BAY806946, Bayer); duvelisib (formerly IPI-145, Infinity Pharmaceuticals); PQR309 (Piqur Therapeutics, Switzerland); and TGR1202 (formerly RP5230, TG Therapeutics).

[00366] In some embodiments, the present invention provides a method of treating AML comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from: FLT3 inhibitors; targeted agents such as IDH inhibitors, anti-CD33 ADCs (e.g. Mylotarg), BCL2 inhibitors, and Hedgehog inhibitors; and chemotherapy such as AraC, daunarubicin, etoposide, methotrexate, fludarabine, mitozantrone, azacytidine, and corticosteroids.

[00367] In some embodiments, the present invention provides a method of treating MDS comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from azacytidine, decitabine and revlimid.

[00368] In some embodiments, the present invention provides a method of treating inflammatory skin conditions such as hidradenitis suppurativa, comprising administering to a patient in need thereof a provided

compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from anti-TNF drugs.

[00369] In some embodiments, the present invention provides a method of treating inflammatory skin conditions such as atopic dermatitis, comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from IL-4/IL-13-targeted agents such as dupilumab.

In some embodiments, the present invention provides a method of treating inflammatory skin conditions such as psoriasis, comprising administering to a patient in need thereof a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents selected from anti-IL-17 and anti-IL-23 antibodies.

[00370] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a cancer, an autoimmune disorder, a proliferative disorder, an inflammatory disorder, a neurodegenerative or neurological disorder, schizophrenia, a bone-related disorder, liver disease, or a cardiac disorder. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[00371] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00372] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00373] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00374] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00375] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00376] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such

as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00377] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00378] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00379] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used

include polymeric substances and waxes.

[00380] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00381] According to one embodiment, the invention relates to a method of inhibiting protein kinase activity or degrading a protein kinase in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00382] According to another embodiment, the invention relates to a method of inhibiting or degrading IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00383] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00384] Inhibition and/or degradation of a protein kinase, or a protein kinase selected from IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[00385] Another embodiment of the present invention relates to a method of degrading a protein kinase and/or inhibiting protein kinase activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[00386] According to another embodiment, the invention relates to a method of degrading and/or inhibiting one or more of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. In other embodiments, the present invention provides a method for treating a disorder mediated by one or more of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present

invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

[00387] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents that are normally administered to treat that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00388] A compound of the current invention may also be used to advantage in combination with other antiproliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; matrix metalloproteinase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (Temodal®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array BioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer and leucovorin.

[00389] The term "aromatase inhibitor" as used herein relates to a compound which inhibits estrogen production, for instance, the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane is marketed under the trade name Aromasin™. Formestane is marketed under the trade name Lentaron™. Fadrozole is marketed under the trade name Afema™. Anastrozole is marketed under the trade name Arimidex™. Letrozole is marketed under the trade names Femara™ or Femar™. Aminoglutethimide is marketed under the trade name Orimeten™. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, such as breast tumors.

[00390] In some embodiments, one or more other therapeutic agent is an mTOR inhibitor, which inhibits cell proliferation, angiogenesis and glucose uptake. In some embodiments, an mTOR inhibitor is everolimus (Afinitor®, Novartis); temsirolimus (Torisel®, Pfizer); and sirolimus (Rapamune®, Pfizer).

[00391] In some embodiments, one or more other therapeutic agent is an aromatase inhibitor. In some embodiments, an aromatase inhibitor is selected from exemestane (Aromasin®, Pfizer); anastazole (Arimidex®, AstraZeneca) and letrozole (Femara®, Novartis).

[00392] The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen is marketed under the trade name Nolvadex™. Raloxifene hydrochloride is marketed under the trade name Evista™. Fulvestrant can be administered under the trade name Faslodex™. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, such as breast tumors.

[00393] The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (Casodex™). The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin can be administered under the trade name Zoladex™.

[00394] The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148. Irinotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark Camptosar™. Topotecan is marketed under the trade name Hycamptin™.

[00395] The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, such as Caelyx™), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide is marketed under the trade name Etopophos™. Teniposide is marketed under the trade name VM 26-Bristol Doxorubicin is marketed under the trade name Acriblastin ™ or Adriamycin™. Epirubicin is marketed under the trade name Farmorubicin™. Idarubicin is marketed. under the trade name Zavedos™. Mitoxantrone is marketed under the trade name Novantron.

[00396] The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing compounds and microtublin polymerization inhibitors including, but not limited to taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine or vinblastine sulfate, vincristine or vincristine sulfate, and vinorelbine; discodermolides; cochicine and epothilones and derivatives thereof. Paclitaxel is marketed under the trade name Taxol™. Docetaxel is marketed under the trade name Taxotere™. Vinblastine sulfate is marketed under the trade name Vinblastin R.P™. Vincristine sulfate is

marketed under the trade name Farmistin™.

[00397] The term "alkylating agent" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide is marketed under the trade name Cyclostin™. Ifosfamide is marketed under the trade name Holoxan™.

[00398] The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes, but is not limited to, suberoylanilide hydroxamic acid (SAHA).

[00399] The term "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine is marketed under the trade name Xeloda™. Gemcitabine is marketed under the trade name Gemzar™.

[00400] The term "platin compound" as used herein includes, but is not limited to, carboplatin, cis-platin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark Carboplat™. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark Eloxatin™.

[00401] The term “Bcl-2 inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against B-cell lymphoma 2 protein (Bcl-2), including but not limited to ABT-199, ABT-731, ABT-737, apogossypol, Ascenta’s pan-Bcl-2 inhibitors, curcumin (and analogs thereof), dual Bcl-2/Bcl-xL inhibitors (Infinity Pharmaceuticals/Novartis Pharmaceuticals), Genasense (G3139), HA14-1 (and analogs thereof; see WO 2008/118802, US 2010/0197686), navitoclax (and analogs thereof, see US 7,390,799), NH-1 (Shenayng Pharmaceutical University), obatoclax (and analogs thereof, see WO 2004/106328, US 2005/0014802), S-001 (Gloria Pharmaceuticals), TW series compounds (Univ. of Michigan), and venetoclax. In some embodiments the Bcl-2 inhibitor is a small molecule therapeutic. In some embodiments the Bcl-2 inhibitor is a peptidomimetic.

[00402] The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, such as a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib, SU101, SU6668 and GFB-111; b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, or

antibodies that target the extracellular domain of IGF-I receptor or its growth factors; d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) compounds targeting, decreasing or inhibiting the activity of the AxI receptor tyrosine kinase family; f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase; g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases, which are part of the PDGFR family, such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, such as imatinib; i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825); j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK/pan-JAK, FAK, PDK1, PKB/Akt, Ras/MAPK, PI3K, SYK, TYK2, BTK and TEC family, and/or members of the cyclin-dependent kinase family (CDK) including staurosporine derivatives, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; llmofosine; RO 318220 and RO 320432; GO 6976; lsis 3521; LY333531/LY379196; isochinoline compounds; FTIs; PD184352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor); k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (Gleevec™) or tyrphostin such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases ($EGFR_1$ ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, such as EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, CP 358774, ZD 1839, ZM 105180; trastuzumab (Herceptin™), cetuximab (Erbitux™), Iressa, Tarceva, OSI-774, Cl-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the

kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF, n) compounds targeting, decreasing or inhibiting the kinase activity of one or more JAK family members (JAK1/JAK2/JAK3/TYK2 and/or pan-JAK), including but not limited to PRT-062070, SB-1578, baricitinib, pacritinib, momelotinib, VX-509, AZD-1480, TG-101348, tofacitinib, and ruxolitinib; o) compounds targeting, decreasing or inhibiting the kinase activity of PI3 kinase (PI3K) including but not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib; and; and q) compounds targeting, decreasing or inhibiting the signaling effects of hedgehog protein (Hh) or smoothened receptor (SMO) pathways, including but not limited to cyclopamine, vismodegib, itraconazole, erismodegib, and IPI-926 (saridegib).

[00403] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g. inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[00404] In some embodiments, one or more other therapeutic agent is a growth factor antagonist, such as an antagonist of platelet-derived growth factor (PDGF), or epidermal growth factor (EGF) or its receptor (EGFR). Approved PDGF antagonists which may be used in the present invention include olaratumab (Lartruvo®; Eli Lilly). Approved EGFR antagonists which may be used in the present invention include cetuximab (Erbitux®, Eli Lilly); necitumumab (Portrazza®, Eli Lilly), panitumumab (Vectibix®, Amgen); and osimertinib (targeting activated EGFR, Tagrisso®, AstraZeneca).

[00405] The term "PI3K inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against one or more enzymes in the phosphatidylinositol-3-kinase family, including, but not limited to PI3Kα, PI3Kγ, PI3Kδ, PI3Kβ, PI3K-C2α, PI3K-C2β, PI3K-C2γ, Vps34, p110-α, p110-β, p110-γ, p110-δ, p85-α, p85-β, p55-γ, p150, p101, and p87. Examples of PI3K inhibitors useful in this invention include but are not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib.

[00406] The term "BTK inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against Bruton's Tyrosine Kinase (BTK), including, but not limited to AVL-292 and ibrutinib.

[00407] The term "SYK inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against spleen tyrosine kinase (SYK), including but not limited to PRT-062070, R-343, R-333, Excellair, PRT-062607, and fostamatinib

[00408] Further examples of BTK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO 2008/039218, US 2008/0108636 and WO 2011/090760, US 2010/0249092, the entirety of each of which is herein incorporated by reference.

[00409] Further examples of SYK inhibitory compounds, and conditions treatable by such compounds

in combination with compounds of this invention can be found in WO 2003/063794, US 2004/0029902, WO 2005/007623, US 2005/0075306, and WO 2006/078846, US 2006/0211657, the entirety of each of which is herein incorporated by reference.

[00410] Further examples of PI3K inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO 2004/019973, US 2004/0106569, WO 2004/089925, US 2004/0242631, US 8,138,347, WO 2002/088112, US 2004/0116421, WO 2007/084786, US 2010/0249126, WO 2007/129161, US 2008/0076768, WO 2006/122806, US 2008/0194579, WO 2005/113554, US 2008/0275067, and WO 2007/044729, US 2010/0087440, the entirety of each of which is herein incorporated by reference.

[00411] Further examples of JAK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO 2009/114512, US 2009/0233903, WO 2008/109943, US 2010/0197671, WO 2007/053452, US 2007/0191405, WO 2001/0142246, US 2001/0053782, and WO 2007/070514, US 2007/0135461, the entirety of each of which is herein incorporated by reference.

[00412] Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (Thalomid™) and TNP-470.

[00413] Examples of proteasome inhibitors useful for use in combination with compounds of the invention include, but are not limited to bortezomib, disulfiram, epigallocatechin-3-gallate (EGCG), salinosporamide A, carfilzomib, ONX-0912, CEP-18770, and MLN9708.

[00414] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g. inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[00415] Compounds which induce cell differentiation processes include, but are not limited to, retinoic acid, α- γ- or δ- tocopherol or α- γ- or δ-tocotrienol.

[00416] The term cyclooxygenase inhibitor as used herein includes, but is not limited to, Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (Celebrex™), rofecoxib (Vioxx™), etoricoxib, valdecoxib or a 5-alkyl-2- arylaminophenylacetic acid, such as 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

[00417] The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. Etridonic acid is marketed under the trade name Didronel™. Clodronic acid is marketed under the trade name Bonefos™. Tiludronic acid is marketed under the trade name Skelid™. Pamidronic acid is marketed under the trade name Aredia™. Alendronic acid is marketed under the trade name Fosamax™. Ibandronic acid is marketed under the trade name Bondranat™. Risedronic acid is marketed under the trade name Actonel™. Zoledronic acid is marketed under the trade name Zometa™. The term "mTOR inhibitors" relates to compounds which

inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

[00418] The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88. The term "biological response modifier" as used herein refers to a lymphokine or interferons.

[00419] The term "inhibitor of Ras oncogenic isoforms", such as H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras; for example, a "farnesyl transferase inhibitor" such as L-744832, DK8G557 or R115777 (Zarnestra™). The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, such as telomestatin.

[00420] The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase include, but are not limited to, bengamide or a derivative thereof.

[00421] The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, but are not limited to, Bortezomib (Velcade™),); carfilzomib (Kyprolis®, Amgen); and ixazomib (Ninlaro®, Takeda), and MLN 341.

[00422] The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251 , BAY 12-9566, TAA211 , MMI270B or AAJ996.

[00423] The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-β-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors, which are compounds which target, decrease or inhibit anaplastic lymphoma kinase.

[00424] Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, such as PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

[00425] The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing

or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[00426] The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1, erbitux, bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

[00427] For the treatment of acute myeloid leukemia (AML), compounds of the current invention can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of the current invention can be administered in combination with, for example, farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

[00428] Other anti-leukemic compounds include, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065 including, but not limited to, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]- amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof and N-hydroxy-3-[4-[(2-hydroxyethyl){2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2- propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt. Somatostatin receptor antagonists as used herein refer to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230. Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in Principles and Practice of Oncology, Devita et al., Eds., 4th Edition, Vol. 1 , pp. 248-275 (1993).

[00429] Also included are EDG binders and ribonucleotide reductase inhibitors. The term "EDG

binders" as used herein refers to a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720. The term "ribonucleotide reductase inhibitors" refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1H-isoindole-1 ,3-dione derivatives.

[00430] Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF such as 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate; Angiostatin™; Endostatin™; anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, such as rhuMAb and RHUFab, VEGF aptamer such as Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, Angiozyme (RPI 4610) and Bevacizumab (Avastin™).

[00431] Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy include treatment with compounds, such as Visudyne™ and porfimer sodium.

[00432] Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone, hydrocortisone, 11-α-epihydrocotisol, cortexolone, 17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

[00433] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[00434] Other chemotherapeutic compounds include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

[00435] The compounds of the invention are also useful as co-therapeutic compounds for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. A compound of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of a compound of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said compound of the invention and said drug substance being in the same or different pharmaceutical composition.

[00436] Suitable anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate; non-steroidal glucocorticoid receptor agonists; LTB4 antagonists such LY293111, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247; LTD4 antagonists such as montelukast and zafirlukast; PDE4 inhibitors such cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering- Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12- 281 (Asta Medica), CDC-801 (Celgene), SeICID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo); A2a agonists; A2b antagonists; and beta-2 adrenoceptor agonists such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol and pharmaceutically acceptable salts thereof. Suitable bronchodilatory drugs include anticholinergic or antimuscarinic compounds, in particular ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate.

[00437] Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine.

[00438] Other useful combinations of compounds of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g. CCR-1 , CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1 , CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH- 55700 and SCH-D, and Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4- aminium chloride (TAK-770).

[00439] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

[00440] A compound of the current invention may also be used in combination with known therapeutic processes, for example, the administration of hormones or radiation. In certain embodiments, a provided compound is used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[00441] A compound of the current invention can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. A compound of the current invention can besides or in addition

be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

[00442] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[00443] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the current invention, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00444] The amount of both an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive compound can be administered.

[00445] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 – 1,000 μg/kg body weight/day of the additional therapeutic agent can be administered.

[00446] The amount of one or more other therapeutic agent present in the compositions of this invention may be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of one or more other therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent. In some embodiments, one or more other therapeutic agent is administered at a dosage of about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% of the amount normally

administered for that agent. As used herein, the phrase "normally administered" means the amount an FDA approved therapeutic agent is approved for dosing per the FDA label insert.

[00447] The compounds of this invention, or pharmaceutical compositions thereof, may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

Exemplary Immuno-Oncology agents

[00448] In some embodiments, one or more other therapeutic agent is an immuno-oncology agent. As used herein, the term "an immuno-oncology agent" refers to an agent which is effective to enhance, stimulate, and/or up-regulate immune responses in a subject. In some embodiments, the administration of an immuno-oncology agent with a compound of the invention has a synergic effect in treating a cancer.

[00449] An immuno-oncology agent can be, for example, a small molecule drug, an antibody, or a biologic or small molecule. Examples of biologic immuno-oncology agents include, but are not limited to, cancer vaccines, antibodies, and cytokines. In some embodiments, an antibody is a monoclonal antibody. In some embodiments, a monoclonal antibody is humanized or human.

[00450] In some embodiments, an immuno-oncology agent is (i) an agonist of a stimulatory (including a co-stimulatory) receptor or (ii) an antagonist of an inhibitory (including a co-inhibitory) signal on T cells, both of which result in amplifying antigen-specific T cell responses.

[00451] Certain of the stimulatory and inhibitory molecules are members of the immunoglobulin super family (IgSF). One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes B7-1, B7-2, B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Another family of membrane bound ligands that bind to co-stimulatory or co-inhibitory receptors is the TNF family of molecules that bind to cognate TNF receptor family members, which includes CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LTβR, LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2, TNFR1, Lymphotoxin α/TNFβ, TNFR2, TNFα, LTβR, Lymphotoxin α1β2, FAS, FASL, RELT, DR6, TROY, NGFR.

[00452] In some embodiments, an immuno-oncology agent is a cytokine that inhibits T cell activation (e.g., IL-6, IL-10, TGF-β, VEGF, and other immunosuppressive cytokines) or a cytokine that stimulates T cell activation, for stimulating an immune response.

[00453] In some embodiments, a combination of a compound of the invention and an immuno-oncology agent can stimulate T cell responses. In some embodiments, an immuno-oncology agent is: (i) an antagonist of a protein that inhibits T cell activation (e.g., immune checkpoint inhibitors) such as CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, and TIM-4; or (ii) an agonist of a protein that stimulates T cell activation such as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40, DR3 and CD28H.

[00454] In some embodiments, an immuno-oncology agent is an antagonist of inhibitory receptors on NK cells or an agonists of activating receptors on NK cells. In some embodiments, an immuno-oncology agent is an antagonists of KIR, such as lirilumab.

[00455] In some embodiments, an immuno-oncology agent is an agent that inhibits or depletes macrophages or monocytes, including but not limited to CSF-1R antagonists such as CSF-1R antagonist antibodies including RG7155 (WO 2011/070024, US 2011/0165156, WO 2011/0107553, US 2012/0329997, WO 2011/131407, US 2013/0005949, WO 2013/087699, US 2014/0336363, WO 2013/119716, WO 2013/132044, US 2014/0079706) or FPA-008 (WO 2011/140249, US 2011/0274683; WO 2013/169264; WO 2014/036357, US 2014/0079699).

[00456] In some embodiments, an immuno-oncology agent is selected from agonistic agents that ligate positive costimulatory receptors, blocking agents that attenuate signaling through inhibitory receptors, antagonists, and one or more agents that increase systemically the frequency of anti-tumor T cells, agents that overcome distinct immune suppressive pathways within the tumor microenvironment (e.g., block inhibitory receptor engagement (e.g., PD-L1/PD-1 interactions), deplete or inhibit Tregs (e.g., using an anti-CD25 monoclonal antibody (e.g., daclizumab) or by ex vivo anti-CD25 bead depletion), inhibit metabolic enzymes such as IDO, or reverse/prevent T cell energy or exhaustion) and agents that trigger innate immune activation and/or inflammation at tumor sites.

[00457] In some embodiments, an immuno-oncology agent is a CTLA-4 antagonist. In some embodiments, a CTLA-4 antagonist is an antagonistic CTLA-4 antibody. In some embodiments, an antagonistic CTLA-4 antibody is YERVOY (ipilimumab) or tremelimumab.

[00458] In some embodiments, an immuno-oncology agent is a PD-1 antagonist. In some embodiments, a PD-1 antagonist is administered by infusion. In some embodiments, an immuno-oncology agent is an antibody or an antigen-binding portion thereof that binds specifically to a Programmed Death-1 (PD-1) receptor and inhibits PD-1 activity. In some embodiments, a PD-1 antagonist is an antagonistic

PD-1 antibody. In some embodiments, an antagonistic PD-1 antibody is OPDIVO (nivolumab), KEYTRUDA (pembrolizumab), or MEDI-0680 (AMP-514; WO2012/145493). In some embodiments, an immuno-oncology agent may be pidilizumab (CT-011). In some embodiments, an immuno-oncology agent is a recombinant protein composed of the extracellular domain of PD-L2 (B7-DC) fused to the Fc portion of IgG1, called AMP-224.

[00459] In some embodiments, an immuno-oncology agent is a PD-L1 antagonist. In some embodiments, a PD-L1 antagonist is an antagonistic PD-L1 antibody. In some embodiments, a PD-L1 antibody is MPDL3280A (RG7446; WO 2010/077634, US 2010/0203056), durvalumab (MEDI4736), BMS-936559 (WO 2007/005874, US 2009/0055944), and MSB0010718C (WO 2013/079174, US 2014/0341917).

[00460] In some embodiments, an immuno-oncology agent is a LAG-3 antagonist. In some embodiments, a LAG-3 antagonist is an antagonistic LAG-3 antibody. In some embodiments, a LAG3 antibody is BMS-986016 (WO 2010/019570, US 2010/0150892, WO 2014/008218, US 2014/0093511), or IMP-731 or IMP-321 (WO 2008/132601, US 2010/0233183, WO 2009/044273, US 2011/0008331).

[00461] In some embodiments, an immuno-oncology agent is a CD137 (4-1BB) agonist. In some embodiments, a CD137 (4-1BB) agonist is an agonistic CD137 antibody. In some embodiments, a CD137 antibody is urelumab or PF-05082566 (WO12/32433).

[00462] In some embodiments, an immuno-oncology agent is a GITR agonist. In some embodiments, a GITR agonist is an agonistic GITR antibody. In some embodiments, a GITR antibody is BMS-986153, BMS-986156, TRX-518 (WO 2006/105021, US 2007/0098719, WO 2009/009116, US 2009/0136494), or MK-4166 (WO 2011/028683, US 2012/0189639).

[00463] In some embodiments, an immuno-oncology agent is an indoleamine (2,3)-dioxygenase (IDO) antagonist. In some embodiments, an IDO antagonist is selected from epacadostat (INCB024360, Incyte); indoximod (NLG-8189, NewLink Genetics Corporation); capmanitib (INC280, Novartis); GDC-0919 (Genentech/Roche); PF-06840003 (Pfizer); BMS:F001287 (Bristol-Myers Squibb); Phy906/KD108 (Phytoceutica); an enzyme that breaks down kynurenine (Kynase, Kyn Therapeutics); and NLG-919 (WO 2009/073620, US 2011/053941, WO 2009/132238, US 2011/136796, WO 2011/056652, US 2012/277217, WO 2012/142237, US 2014/066625).

[00464] In some embodiments, an immuno-oncology agent is an OX40 agonist. In some embodiments, an OX40 agonist is an agonistic OX40 antibody. In some embodiments, an OX40 antibody is MEDI-6383 or MEDI-6469.

[00465] In some embodiments, an immuno-oncology agent is an OX40L antagonist. In some embodiments, an OX40L antagonist is an antagonistic OX40 antibody. In some embodiments, an OX40L antagonist is RG-7888 (WO 2006/029879, US 7,501,496).

[00466] In some embodiments, an immuno-oncology agent is a CD40 agonist. In some embodiments, a CD40 agonist is an agonistic CD40 antibody. In some embodiments, an immuno-oncology agent is a CD40 antagonist. In some embodiments, a CD40 antagonist is an antagonistic CD40 antibody. In some embodiments, a CD40 antibody is lucatumumab or dacetuzumab.

[00467] In some embodiments, an immuno-oncology agent is a CD27 agonist. In some embodiments, a CD27 agonist is an agonistic CD27 antibody. In some embodiments, a CD27 antibody is varlilumab.

[00468] In some embodiments, an immuno-oncology agent is MGA271 (to B7H3) (WO 2011/109400, US 2013/0149236).

[00469] In some embodiments, an immuno-oncology agent is abagovomab, adecatumumab, afutuzumab, alemtuzumab, anatumomab mafenatox, apolizumab, atezolimab, avelumab, blinatumomab, BMS-936559, catumaxomab, durvalumab, epacadostat, epratuzumab, indoximod, inotuzumab ozogamicin, intelumumab, ipilimumab, isatuximab, lambrolizumab, MED14736, MPDL3280A, nivolumab, obinutuzumab, ocaratuzumab, ofatumumab, olatatumab, pembrolizumab, pidilizumab, rituximab, ticilimumab, samalizumab, or tremelimumab.

[00470] In some embodiments, an immuno-oncology agent is an immunostimulatory agent. For example, antibodies blocking the PD-1 and PD-L1 inhibitory axis can unleash activated tumor-reactive T cells and have been shown in clinical trials to induce durable anti-tumor responses in increasing numbers of tumor histologies, including some tumor types that conventionally have not been considered immunotherapy sensitive. See, e.g., Okazaki, T. *et al.* (2013) Nat. Immunol. 14, 1212–1218; Zou *et al.* (2016) Sci. Transl. Med. 8. The anti-PD-1 antibody nivolumab (Opdivo®, Bristol-Myers Squibb, also known as ONO-4538, MDX1106 and BMS-936558), has shown potential to improve the overall survival in patients with RCC who had experienced disease progression during or after prior anti-angiogenic therapy.

[00471] In some embodiments, the immunomodulatory therapeutic specifically induces apoptosis of tumor cells. Approved immunomodulatory therapeutics which may be used in the present invention include pomalidomide (Pomalyst®, Celgene); lenalidomide (Revlimid®, Celgene); ingenol mebutate (Picato®, LEO Pharma).

[00472] In some embodiments, an immuno-oncology agent is a cancer vaccine. In some embodiments, the cancer vaccine is selected from sipuleucel-T (Provenge®, Dendreon/Valeant Pharmaceuticals), which has been approved for treatment of asymptomatic, or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer; and talimogene laherparepvec (Imlygic®, BioVex/Amgen, previously known as T-VEC), a genetically modified oncolytic viral therapy approved for treatment of unresectable cutaneous, subcutaneous and nodal lesions in melanoma. In some embodiments, an immuno-oncology agent is selected from an oncolytic viral therapy such as pexastimogene devacirepvec (PexaVec/JX-594, SillaJen/formerly Jennerex Biotherapeutics), a thymidine kinase- (TK-) deficient

vaccinia virus engineered to express GM-CSF, for hepatocellular carcinoma (NCT02562755) and melanoma (NCT00429312); pelareorep (Reolysin®, Oncolytics Biotech), a variant of respiratory enteric orphan virus (reovirus) which does not replicate in cells that are not RAS-activated, in numerous cancers, including colorectal cancer (NCT01622543); prostate cancer (NCT01619813); head and neck squamous cell cancer (NCT01166542); pancreatic adenocarcinoma (NCT00998322); and non-small cell lung cancer (NSCLC) (NCT 00861627); enadenotucirev (NG-348, PsiOxus, formerly known as ColoAd1), an adenovirus engineered to express a full length CD80 and an antibody fragment specific for the T-cell receptor CD3 protein, in ovarian cancer (NCT02028117); metastatic or advanced epithelial tumors such as in colorectal cancer, bladder cancer, head and neck squamous cell carcinoma and salivary gland cancer (NCT02636036); ONCOS-102 (Targovax/formerly Oncos), an adenovirus engineered to express GM-CSF, in melanoma (NCT03003676); and peritoneal disease, colorectal cancer or ovarian cancer (NCT02963831); GL-ONC1 (GLV-1h68/GLV-1h153, Genelux GmbH), vaccinia viruses engineered to express beta-galactosidase (beta-gal)/beta-glucoronidase or beta-gal/human sodium iodide symporter (hNIS), respectively, were studied in peritoneal carcinomatosis (NCT01443260); fallopian tube cancer, ovarian cancer (NCT 02759588); or CG0070 (Cold Genesys), an adenovirus engineered to express GM-CSF, in bladder cancer (NCT02365818).

[00473] In some embodiments, an immuno-oncology agent is selected from JX-929 (SillaJen/formerly Jennerex Biotherapeutics), a TK- and vaccinia growth factor-deficient vaccinia virus engineered to express cytosine deaminase, which is able to convert the prodrug 5-fluorocytosine to the cytotoxic drug 5-fluorouracil; TG01 and TG02 (Targovax/formerly Oncos), peptide-based immunotherapy agents targeted for difficult-to-treat RAS mutations; and TILT-123 (TILT Biotherapeutics), an engineered adenovirus designated: Ad5/3-E2F-delta24-hTNFα-IRES-hIL20; and VSV-GP (ViraTherapeutics) a vesicular stomatitis virus (VSV) engineered to express the glycoprotein (GP) of lymphocytic choriomeningitis virus (LCMV), which can be further engineered to express antigens designed to raise an antigen-specific $CD8^+$ T cell response.

[00474] In some embodiments, an immuno-oncology agent is a T-cell engineered to express a chimeric antigen receptor, or CAR. The T-cells engineered to express such chimeric antigen receptor are referred to as a CAR-T cells.

[00475] CARs have been constructed that consist of binding domains, which may be derived from natural ligands, single chain variable fragments (scFv) derived from monoclonal antibodies specific for cell-surface antigens, fused to endodomains that are the functional end of the T-cell receptor (TCR), such as the CD3-zeta signaling domain from TCRs, which is capable of generating an activation signal in T lymphocytes. Upon antigen binding, such CARs link to endogenous signaling pathways in the effector cell and generate activating signals similar to those initiated by the TCR complex.

[00476] For example, in some embodiments the CAR-T cell is one of those described in U.S. Patent 8,906,682, the entirety of each of which is herein incorporated by reference, which discloses CAR-T cells engineered to comprise an extracellular domain having an antigen binding domain (such as a domain that binds to CD19), fused to an intracellular signaling domain of the T cell antigen receptor complex zeta chain (such as CD3 zeta). When expressed in the T cell, the CAR is able to redirect antigen recognition based on the antigen binding specificity. In the case of CD19, the antigen is expressed on malignant B cells. Over 200 clinical trials are currently in progress employing CAR-T in a wide range of indications. [https://clinicaltrials.gov/ct2/results?term=chimeric+antigen+receptors&pg=1].

[00477] In some embodiments, an immunostimulatory agent is an activator of retinoic acid receptor-related orphan receptor γ (RORγt). RORγt is a transcription factor with key roles in the differentiation and maintenance of Type 17 effector subsets of CD4+ (Th17) and CD8+ (Tc17) T cells, as well as the differentiation of IL-17 expressing innate immune cell subpopulations such as NK cells. In some embodiments, an activator of RORγt is LYC-55716 (Lycera), which is currently being evaluated in clinical trials for the treatment of solid tumors (NCT02929862).

[00478] In some embodiments, an immunostimulatory agent is an agonist or activator of a toll-like receptor (TLR). Suitable activators of TLRs include an agonist or activator of TLR9 such as SD-101 (Dynavax). SD-101 is an immunostimulatory CpG which is being studied for B-cell, follicular and other lymphomas (NCT02254772). Agonists or activators of TLR8 which may be used in the present invention include motolimod (VTX-2337, VentiRx Pharmaceuticals) which is being studied for squamous cell cancer of the head and neck (NCT02124850) and ovarian cancer (NCT02431559).

[00479] Other immuno-oncology agents that may be used in the present invention include urelumab (BMS-663513, Bristol-Myers Squibb), an anti-CD137 monoclonal antibody; varlilumab (CDX-1127, Celldex Therapeutics), an anti-CD27 monoclonal antibody; BMS-986178 (Bristol-Myers Squibb), an anti-OX40 monoclonal antibody; lirilumab (IPH2102/BMS-986015, Innate Pharma, Bristol-Myers Squibb), an anti-KIR monoclonal antibody; monalizumab (IPH2201, Innate Pharma, AstraZeneca) an anti-NKG2A monoclonal antibody; andecaliximab (GS-5745, Gilead Sciences), an anti-MMP9 antibody; MK-4166 (Merck & Co.), an anti-GITR monoclonal antibody.

[00480] In some embodiments, an immunostimulatory agent is selected from elotuzumab, mifamurtide, an agonist or activator of a toll-like receptor, and an activator of RORγt.

[00481] In some embodiments, an immunostimulatory therapeutic is recombinant human interleukin 15 (rhIL-15). rhIL-15 has been tested in the clinic as a therapy for melanoma and renal cell carcinoma (NCT01021059 and NCT01369888) and leukemias (NCT02689453). In some embodiments, an immunostimulatory agent is recombinant human interleukin 12 (rhIL-12). In some embodiments, an IL-15

based immunotherapeutic is heterodimeric IL-15 (hetIL-15, Novartis/Admune), a fusion complex composed of a synthetic form of endogenous IL-15 complexed to the soluble IL-15 binding protein IL-15 receptor alpha chain (IL15:sIL-15RA), which has been tested in Phase 1 clinical trials for melanoma, renal cell carcinoma, non-small cell lung cancer and head and neck squamous cell carcinoma (NCT02452268). In some embodiments, a recombinant human interleukin 12 (rhIL-12) is NM-IL-12 (Neumedicines, Inc.), NCT02544724, or NCT02542124.

[00482] In some embodiments, an immuno-oncology agent is selected from those descripted in Jerry L. Adams ET. AL., "Big opportunities for small molecules in immuno-oncology," Cancer Therapy **2015**, Vol. 14, pages 603-622, the content of which is incorporated herein by reference in its entirety. In some embodiment, an immuno-oncology agent is selected from the examples described in Table 1 of Jerry L. Adams ET. AL. In some embodiments, an immuno-oncology agent is a small molecule targeting an immuno-oncology target selected from those listed in Table 2 of Jerry L. Adams ET. AL. In some embodiments, an immuno-oncology agent is a small molecule agent selected from those listed in Table 2 of Jerry L. Adams ET. AL.

[00483] In some embodiments, an immuno-oncology agent is selected from the small molecule immuno-oncology agents described in Peter L. Toogood, "Small molecule immuno-oncology therapeutic agents," Bioorganic & Medicinal Chemistry Letters 2018, Vol. 28, pages 319-329, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is an agent targeting the pathways as described in Peter L. Toogood.

[00484] In some embodiments, an immuno-oncology agent is selected from those described in Sandra L. Ross et al., "Bispecific T cell engager (BiTE®) antibody constructs can mediate bystander tumor cell killing", PLoS ONE 12(8): e0183390, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is a bispecific T cell engager (BiTE®) antibody construct. In some embodiments, a bispecific T cell engager (BiTE®) antibody construct is a CD19/CD3 bispecific antibody construct. In some embodiments, a bispecific T cell engager (BiTE®) antibody construct is an EGFR/CD3 bispecific antibody construct. In some embodiments, a bispecific T cell engager (BiTE®) antibody construct activates T cells. In some embodiments, a bispecific T cell engager (BiTE®) antibody construct activates T cells, which release cytokines inducing upregulation of intercellular adhesion molecule 1 (ICAM-1) and FAS on bystander cells. In some embodiments, a bispecific T cell engager (BiTE®) antibody construct activates T cells which result in induced bystander cell lysis. In some embodiments, the bystander cells are in solid tumors. In some embodiments, the bystander cells being lysed are in proximity to the BiTE®-activated T cells. In some embodiment, the bystander cells comprises tumor-associated antigen (TAA) negative cancer cells. In some embodiment, the bystander cells comprise EGFR-negative cancer cells. In some embodiments, an immuno-oncology agent is an antibody which

blocks the PD-L1/PD1 axis and/or CTLA4. In some embodiments, an immuno-oncology agent is an ex-vivo expanded tumor-infiltrating T cell. In some embodiments, an immuno-oncology agent is a bispecific antibody construct or chimeric antigen receptors (CARs) that directly connect T cells with tumor-associated surface antigens (TAAs).

Exemplary Immune Checkpoint Inhibitors

[00485] In some embodiments, an immuno-oncology agent is an immune checkpoint inhibitor as described herein.

[00486] The term "checkpoint inhibitor" as used herein relates to agents useful in preventing cancer cells from avoiding the immune system of the patient. One of the major mechanisms of anti-tumor immunity subversion is known as "T-cell exhaustion," which results from chronic exposure to antigens that has led to up-regulation of inhibitory receptors. These inhibitory receptors serve as immune checkpoints in order to prevent uncontrolled immune reactions.

[00487] PD-1 and co-inhibitory receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA-4, B and T Lymphocyte Attenuator (BTLA; CD272), T cell Immunoglobulin and Mucin domain-3 (Tim-3), Lymphocyte Activation Gene-3 (Lag-3; CD223), and others are often referred to as a checkpoint regulators. They act as molecular "gatekeepers" that allow extracellular information to dictate whether cell cycle progression and other intracellular signaling processes should proceed.

[00488] In some embodiments, an immune checkpoint inhibitor is an antibody to PD-1. PD-1 binds to the programmed cell death 1 receptor (PD-1) to prevent the receptor from binding to the inhibitory ligand PDL-1, thus overriding the ability of tumors to suppress the host anti-tumor immune response.

[00489] In one aspect, the checkpoint inhibitor is a biologic therapeutic or a small molecule. In another aspect, the checkpoint inhibitor is a monoclonal antibody, a humanized antibody, a fully human antibody, a fusion protein or a combination thereof. In a further aspect, the checkpoint inhibitor inhibits a checkpoint protein selected from CTLA-4, PDLl, PDL2, PDl, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In an additional aspect, the checkpoint inhibitor interacts with a ligand of a checkpoint protein selected from CTLA-4, PDLl, PDL2, PDl, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In an aspect, the checkpoint inhibitor is an immunostimulatory agent, a T cell growth factor, an interleukin, an antibody, a vaccine or a combination thereof. In a further aspect, the interleukin is IL-7 or IL-15. In a specific aspect, the interleukin is glycosylated IL-7. In an additional aspect, the vaccine is a dendritic cell (DC) vaccine.

[00490] Checkpoint inhibitors include any agent that blocks or inhibits in a statistically significant manner, the inhibitory pathways of the immune system. Such inhibitors may include small molecule inhibitors or may include antibodies, or antigen binding fragments thereof, that bind to and block or inhibit immune checkpoint receptors or antibodies that bind to and block or inhibit immune checkpoint receptor ligands. Illustrative checkpoint molecules that may be targeted for blocking or inhibition include, but are not limited to, CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, GAL9, LAG3, TIM3, VISTA, KIR, 2B4 (belongs to the CD2 family of molecules and is expressed on all NK, γδ, and memory $CD8^+$ (αβ) T cells), CD160 (also referred to as BY55), CGEN-15049, CHK 1 and CHK2 kinases, A2aR, and various B-7 family ligands. B7 family ligands include, but are not limited to, B7- 1, B7-2, B7-DC, B7-H1, B7-H2, B7-H3, B7-H4, B7-H5, B7-H6 and B7-H7. Checkpoint inhibitors include antibodies, or antigen binding fragments thereof, other binding proteins, biologic therapeutics, or small molecules, that bind to and block or inhibit the activity of one or more of CTLA-4, PDL1, PDL2, PD1, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD 160 and CGEN-15049. Illustrative immune checkpoint inhibitors include Tremelimumab (CTLA-4 blocking antibody), anti-OX40, PD-Ll monoclonal Antibody (Anti-B7-Hl; MEDI4736), MK-3475 (PD-1 blocker), Nivolumab (anti-PDl antibody), CT-011 (anti-PDl antibody), BY55 monoclonal antibody, AMP224 (anti-PDLl antibody), BMS- 936559 (anti-PDLl antibody), MPLDL3280A (anti-PDLl antibody), MSB0010718C (anti-PDLl antibody), and ipilimumab (anti-CTLA-4 checkpoint inhibitor). Checkpoint protein ligands include, but are not limited to PD-Ll, PD-L2, B7-H3, B7-H4, CD28, CD86 and TIM-3.

[00491] In certain embodiments, the immune checkpoint inhibitor is selected from a PD-1 antagonist, a PD-L1 antagonist, and a CTLA-4 antagonist. In some embodiments, the checkpoint inhibitor is selected from the group consisting of nivolumab (Opdivo®), ipilimumab (Yervoy®), and pembrolizumab (Keytruda®). In some embodiments, the checkpoint inhibitor is selected from nivolumab (anti-PD-1 antibody, Opdivo®, Bristol-Myers Squibb); pembrolizumab (anti-PD-1 antibody, Keytruda®, Merck); ipilimumab (anti-CTLA-4 antibody, Yervoy®, Bristol-Myers Squibb); durvalumab (anti-PD-L1 antibody, Imfinzi®, AstraZeneca); and atezolizumab (anti-PD-L1 antibody, Tecentriq®, Genentech).

[00492] In some embodiments, the checkpoint inhibitor is selected from the group consisting of lambrolizumab (MK-3475), nivolumab (BMS-936558), pidilizumab (CT-011), AMP-224, MDX-1105, MEDI4736, MPDL3280A, BMS-936559, ipilimumab, lirlumab, IPH2101, pembrolizumab (Keytruda®), and tremelimumab.

[00493] In some embodiments, an immune checkpoint inhibitor is REGN2810 (Regeneron), an anti-PD-1 antibody tested in patients with basal cell carcinoma (NCT03132636); NSCLC (NCT03088540); cutaneous squamous cell carcinoma (NCT02760498); lymphoma (NCT02651662); and melanoma (NCT03002376); pidilizumab (CureTech), also known as CT-011, an antibody that binds to PD-1, in clinical

trials for diffuse large B-cell lymphoma and multiple myeloma; avelumab (Bavencio®, Pfizer/Merck KGaA), also known as MSB0010718C), a fully human IgG1 anti-PD-L1 antibody, in clinical trials for non-small cell lung cancer, Merkel cell carcinoma, mesothelioma, solid tumors, renal cancer, ovarian cancer, bladder cancer, head and neck cancer, and gastric cancer; or PDR001 (Novartis), an inhibitory antibody that binds to PD-1, in clinical trials for non-small cell lung cancer, melanoma, triple negative breast cancer and advanced or metastatic solid tumors. Tremelimumab (CP-675,206; Astrazeneca) is a fully human monoclonal antibody against CTLA-4 that has been in studied in clinical trials for a number of indications, including: mesothelioma, colorectal cancer, kidney cancer, breast cancer, lung cancer and non-small cell lung cancer, pancreatic ductal adenocarcinoma, pancreatic cancer, germ cell cancer, squamous cell cancer of the head and neck, hepatocellular carcinoma, prostate cancer, endometrial cancer, metastatic cancer in the liver, liver cancer, large B-cell lymphoma, ovarian cancer, cervical cancer, metastatic anaplastic thyroid cancer, urothelial cancer, fallopian tube cancer, multiple myeloma, bladder cancer, soft tissue sarcoma, and melanoma. AGEN-1884 (Agenus) is an anti-CTLA4 antibody that is being studied in Phase 1 clinical trials for advanced solid tumors (NCT02694822).

[00494] In some embodiments, a checkpoint inhibitor is an inhibitor of T-cell immunoglobulin mucin containing protein-3 (TIM-3). TIM-3 inhibitors that may be used in the present invention include TSR-022, LY3321367 and MBG453. TSR-022 (Tesaro) is an anti-TIM-3 antibody which is being studied in solid tumors (NCT02817633). LY3321367 (Eli Lilly) is an anti-TIM-3 antibody which is being studied in solid tumors (NCT03099109). MBG453 (Novartis) is an anti-TIM-3 antibody which is being studied in advanced malignancies (NCT02608268).

[00495] In some embodiments, a checkpoint inhibitor is an inhibitor of T cell immunoreceptor with Ig and ITIM domains, or TIGIT, an immune receptor on certain T cells and NK cells. TIGIT inhibitors that may be used in the present invention include BMS-986207 (Bristol-Myers Squibb), an anti-TIGIT monoclonal antibody (NCT02913313); OMP-313M32 (Oncomed); and anti-TIGIT monoclonal antibody (NCT03119428).

[00496] In some embodiments, a checkpoint inhibitor is an inhibitor of Lymphocyte Activation Gene-3 (LAG-3). LAG-3 inhibitors that may be used in the present invention include BMS-986016 and REGN3767 and IMP321. BMS-986016 (Bristol-Myers Squibb), an anti-LAG-3 antibody, is being studied in glioblastoma and gliosarcoma (NCT02658981). REGN3767 (Regeneron), is also an anti-LAG-3 antibody, and is being studied in malignancies (NCT03005782). IMP321 (Immutep S.A.) is an LAG-3-Ig fusion protein, being studied in melanoma (NCT02676869); adenocarcinoma (NCT02614833); and metastatic breast cancer (NCT00349934).

[00497] Checkpoint inhibitors that may be used in the present invention include OX40 agonists. OX40 agonists that are being studied in clinical trials include PF-04518600/PF-8600 (Pfizer), an agonistic anti-

OX40 antibody, in metastatic kidney cancer (NCT03092856) and advanced cancers and neoplasms (NCT02554812; NCT05082566); GSK3174998 (Merck), an agonistic anti-OX40 antibody, in Phase 1 cancer trials (NCT02528357); MEDI0562 (Medimmune/AstraZeneca), an agonistic anti-OX40 antibody, in advanced solid tumors (NCT02318394 and NCT02705482); MEDI6469, an agonistic anti-OX40 antibody (Medimmune/AstraZeneca), in patients with colorectal cancer (NCT02559024), breast cancer (NCT01862900), head and neck cancer (NCT02274155) and metastatic prostate cancer (NCT01303705); and BMS-986178 (Bristol-Myers Squibb) an agonistic anti-OX40 antibody, in advanced cancers (NCT02737475).

[00498] Checkpoint inhibitors that may be used in the present invention include CD137 (also called 4-1BB) agonists. CD137 agonists that are being studied in clinical trials include utomilumab (PF-05082566, Pfizer) an agonistic anti-CD137 antibody, in diffuse large B-cell lymphoma (NCT02951156) and in advanced cancers and neoplasms (NCT02554812 and NCT05082566); urelumab (BMS-663513, Bristol-Myers Squibb), an agonistic anti-CD137 antibody, in melanoma and skin cancer (NCT02652455) and glioblastoma and gliosarcoma (NCT02658981).

[00499] Checkpoint inhibitors that may be used in the present invention include CD27 agonists. CD27 agonists that are being studied in clinical trials include varlilumab (CDX-1127, Celldex Therapeutics) an agonistic anti-CD27 antibody, in squamous cell head and neck cancer, ovarian carcinoma, colorectal cancer, renal cell cancer, and glioblastoma (NCT02335918); lymphomas (NCT01460134); and glioma and astrocytoma (NCT02924038).

[00500] Checkpoint inhibitors that may be used in the present invention include glucocorticoid-induced tumor necrosis factor receptor (GITR) agonists. GITR agonists that are being studied in clinical trials include TRX518 (Leap Therapeutics), an agonistic anti-GITR antibody, in malignant melanoma and other malignant solid tumors (NCT01239134 and NCT02628574); GWN323 (Novartis), an agonistic anti-GITR antibody, in solid tumors and lymphoma (NCT 02740270); INCAGN01876 (Incyte/Agenus), an agonistic anti-GITR antibody, in advanced cancers (NCT02697591 and NCT03126110); MK-4166 (Merck), an agonistic anti-GITR antibody, in solid tumors (NCT02132754) and MEDI1873 (Medimmune/AstraZeneca), an agonistic hexameric GITR-ligand molecule with a human IgG1 Fc domain, in advanced solid tumors (NCT02583165).

[00501] Checkpoint inhibitors that may be used in the present invention include inducible T-cell co-stimulator (ICOS, also known as CD278) agonists. ICOS agonists that are being studied in clinical trials include MEDI-570 (Medimmune), an agonistic anti-ICOS antibody, in lymphomas (NCT02520791); GSK3359609 (Merck), an agonistic anti-ICOS antibody, in Phase 1 (NCT02723955); JTX-2011 (Jounce Therapeutics), an agonistic anti-ICOS antibody, in Phase 1 (NCT02904226).

[00502] Checkpoint inhibitors that may be used in the present invention include killer IgG-like receptor (KIR) inhibitors. KIR inhibitors that are being studied in clinical trials include lirilumab (IPH2102/BMS-986015, Innate Pharma/Bristol-Myers Squibb), an anti-KIR antibody, in leukemias (NCT01687387, NCT02399917, NCT02481297, NCT02599649), multiple myeloma (NCT02252263), and lymphoma (NCT01592370); IPH2101 (1-7F9, Innate Pharma) in myeloma (NCT01222286 and NCT01217203); and IPH4102 (Innate Pharma), an anti-KIR antibody that binds to three domains of the long cytoplasmic tail (KIR3DL2), in lymphoma (NCT02593045).

[00503] Checkpoint inhibitors that may be used in the present invention include CD47 inhibitors of interaction between CD47 and signal regulatory protein alpha (SIRPa). CD47/SIRPa inhibitors that are being studied in clinical trials include ALX-148 (Alexo Therapeutics), an antagonistic variant of (SIRPa) that binds to CD47 and prevents CD47/SIRPa-mediated signaling, in phase 1 (NCT03013218); TTI-621 (SIRPa-Fc, Trillium Therapeutics), a soluble recombinant fusion protein created by linking the N-terminal CD47-binding domain of SIRPa with the Fc domain of human IgG1, acts by binding human CD47, and preventing it from delivering its "do not eat" signal to macrophages, is in clinical trials in Phase 1 (NCT02890368 and NCT02663518); CC-90002 (Celgene), an anti-CD47 antibody, in leukemias (NCT02641002); and Hu5F9-G4 (Forty Seven, Inc.), in colorectal neoplasms and solid tumors (NCT02953782), acute myeloid leukemia (NCT02678338) and lymphoma (NCT02953509).

[00504] Checkpoint inhibitors that may be used in the present invention include CD73 inhibitors. CD73 inhibitors that are being studied in clinical trials include MEDI9447 (Medimmune), an anti-CD73 antibody, in solid tumors (NCT02503774); and BMS-986179 (Bristol-Myers Squibb), an anti-CD73 antibody, in solid tumors (NCT02754141).

[00505] Checkpoint inhibitors that may be used in the present invention include agonists of stimulator of interferon genes protein (STING, also known as transmembrane protein 173, or TMEM173). Agonists of STING that are being studied in clinical trials include MK-1454 (Merck), an agonistic synthetic cyclic dinucleotide, in lymphoma (NCT03010176); and ADU-S100 (MIW815, Aduro Biotech/Novartis), an agonistic synthetic cyclic dinucleotide, in Phase 1 (NCT02675439 and NCT03172936).

[00506] Checkpoint inhibitors that may be used in the present invention include CSF1R inhibitors. CSF1R inhibitors that are being studied in clinical trials include pexidartinib (PLX3397, Plexxikon), a CSF1R small molecule inhibitor, in colorectal cancer, pancreatic cancer, metastatic and advanced cancers (NCT02777710) and melanoma, non-small cell lung cancer, squamous cell head and neck cancer, gastrointestinal stromal tumor (GIST) and ovarian cancer (NCT02452424); and IMC-CS4 (LY3022855, Lilly), an anti-CSF-1R antibody, in pancreatic cancer (NCT03153410), melanoma (NCT03101254), and solid tumors (NCT02718911); and BLZ945 (4-[2((1R,2R)-2-hydroxycyclohexylamino)-benzothiazol-6-

yloxyl]-pyridine-2-carboxylic acid methylamide, Novartis), an orally available inhibitor of CSF1R, in advanced solid tumors (NCT02829723).

[00507] Checkpoint inhibitors that may be used in the present invention include NKG2A receptor inhibitors. NKG2A receptor inhibitors that are being studied in clinical trials include monalizumab (IPH2201, Innate Pharma), an anti-NKG2A antibody, in head and neck neoplasms (NCT02643550) and chronic lymphocytic leukemia (NCT02557516).

[00508] In some embodiments, the immune checkpoint inhibitor is selected from nivolumab, pembrolizumab, ipilimumab, avelumab, durvalumab, atezolizumab, or pidilizumab.

EXEMPLIFICATION

[00509] **Abbreviations**

Ac: acetyl

AcOH: acetic acid

ACN: acetonitrile

Ad: adamantly

AIBN: 2,2'-azo bisisobutyronitrile

Anhyd: anhydrous

Aq: aqueous

B_2Pin_2: bis (pinacolato)diboron -4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane)

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

BH_3: Borane

Bn: benzyl

Boc: *tert*-butoxycarbonyl

Boc_2O: di-tert-butyl dicarbonate

BPO: benzoyl peroxide

^{n}BuOH: n-butanol

CDI: carbonyldiimidazole

COD: cyclooctadiene

d: days

DABCO: 1,4-diazobicyclo[2.2.2]octane

DAST: diethylaminosulfur trifluoride

dba: dibenzylideneacetone

DBU: 1,8-diazobicyclo[5.4.0]undec-7-ene

DCE: 1,2-dichloroethane

DCM: dichloromethane

DEA: diethylamine

DHP: dihydropyran

DIBAL-H: diisobutylaluminum hydride

DIPA: diisopropylamine

DIPEA or DIEA: N,N-diisopropylethylamine

DMA: N,N-dimethylacetamide

DME: 1,2-dimethoxyethane

DMAP: 4-dimethylaminopyridine

DMF: N,N-dimethylformamide

DMP: Dess-Martin periodinane

DMSO-dimethyl sulfoxide

DPPA: diphenylphosphoryl azide

dppf: 1,1'-bis(diphenylphosphino)ferrocene

EDC or EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

ee: enantiomeric excess

ESI: electrospray ionization

EA: ethyl acetate

EtOAc: ethyl acetate

EtOH: ethanol

FA: formic acid

h or hrs: hours

HATU: N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate

HCl: hydrochloric acid

HPLC: high performance liquid chromatography

HOAc: acetic acid

IBX: 2-iodoxybenzoic acid

IPA: isopropyl alcohol

KHMDS: potassium hexamethyldisilazide

K_2CO_3: potassium carbonate

LAH: lithium aluminum hydride

LDA: lithium diisopropylamide

m-CPBA: meta-chloroperbenzoic acid

M: molar

MeCN: acetonitrile

MeOH: methanol

Me_2S: dimethyl sulfide

MeONa: sodium methylate

MeI: iodomethane

min: minutes

mL: milliliters

mM: millimolar

mmol: millimoles

MPa: mega pascal

MOMCl: methyl chloromethyl ether

MsCl: methanesulfonyl chloride

MTBE: methyl *tert*-butyl ether

nBuLi: n-butyllithium

$NaNO_2$: sodium nitrite

NaOH: sodium hydroxide

Na_2SO_4: sodium sulfate

NBS: N-bromosuccinimide

NCS: N-chlorosuccinimide

NFSI: N-Fluorobenzenesulfonimide

NMO: N-methylmorpholine N-oxide

NMP: N-methylpyrrolidine

NMR: Nuclear Magnetic Resonance

^oC: degrees Celsius

Pd/C: Palladium on Carbon

$Pd(OAc)_2$: Palladium Acetate

PBS: phosphate buffered saline

PE: petroleum ether

$POCl_3$: phosphorus oxychloride

PPh_3: triphenylphosphine

PyBOP: (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

Rel: relative

R.T. or rt: room temperature

sat: saturated

SEMCl: chloromethyl-2-trimethylsilylethyl ether

SFC: supercritical fluid chromatography

$SOCl_2$: sulfur dichloride

tBuOK: potassium *tert*-butoxide

TBAB: tetrabutylammonium bromide

TBAI: tetrabutylammonium iodide

TEA: triethylamine

Tf: trifluoromethanesulfonate

TfAA, TFMSA or Tf_2O: trifluoromethanesulfonic anhydride

TFA: trifluoracetic acid

TIPS: triisopropylsilyl

THF: tetrahydrofuran

THP: tetrahydropyran

TLC: thin layer chromatography

TMEDA: tetramethylethylenediamine

pTSA: para-toluenesulfonic acid

wt: weight

Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

General Synthetic Methods

[00510] The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations were performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials was confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations used are those conventional in the art.

[00511] All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention were either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

[00512] All reactions were carried out under nitrogen or argon unless otherwise stated.

[00513] Proton NMR (^{1}H NMR) was conducted in deuterated solvent. In certain compounds disclosed

herein, one or more ^{1}H shifts overlap with residual proteo solvent signals; these signals have not been reported in the experimental provided hereinafter.

Table 2: Analytical instruments

LCMS	Shimadzu UFLC MS: LCMS-2020 Agilent Technologies 1200 series MS: Agilent Technologies 6110 Agilent Technologies 1200 series MS: LC/MSD VL
NMR	BRUKER AVANCE III/400; Frequency (MHz) 400.13; Nucleus: 1H; Number of Transients: 8
Prep-HPLC	Gilson GX-281 systems: instruments GX-A, GX-B, GX-C, GX-D, GX-E, GX-F, GX-G and GX-H
GCMS	SHIMADZU GCMS-QP2010 Ultra
Analytical cSFC	Agilent Technologies 1290 Infinity
Prep-cSFC	Waters SFC Prep 80

[00514] For acidic LCMS data: LCMS was recorded on an Agilent 1200 Series LC/MSD or Shimadzu LCMS2020 equipped with electro-spray ionization and quadruple MS detector [ES+ve to give MH^{+}] and equipped with Chromolith Flash RP-18e 25*2.0 mm, eluting with 0.0375 vol% TFA in water (solvent A) and 0.01875 vol% TFA in acetonitrile (solvent B). Other LCMS was recorded on an Agilent 1290 Infinity RRLC attached with Agilent 6120 Mass detector. The column used was BEH C18 50*2.1 mm, 1.7 micron. Column flow was 0.55 ml /min and mobile phase are used (A) 2 mM Ammonium Acetate in 0.1% Formic Acid in Water and (B) 0.1 % Formic Acid in Acetonitrile.

[00515] For basic LCMS data: LCMS was recorded on an Agilent 1200 Series LC/MSD or Shimadzu LCMS 2020 equipped with electro-spray ionization and quadruple MS detector [ES+ve to give MH^{+}] and equipped with Xbridge C18, 2.1X50 mm columns packed with 5 mm C18-coated silica or Kinetex EVO C18 2.1X30mm columns packed with 5 mm C18-coated silica, eluting with 0.05 vol% $NH_3 \cdot H_2O$ in water (solvent A) and acetonitrile (solvent B).

[00516] HPLC Analytical Method: HPLC was carried out on X Bridge C18 150*4.6 mm, 5 micron. Column flow is 1.0 ml /min and mobile phase are used (A) 0.1 % Ammonia in water and (B) 0.1 % Ammonia in Acetonitrile.

[00517] Prep HPLC Analytical Method: The compound was purified on Shimadzu LC-20AP and UV detector. The column used was X-BRIDGE C18 (250*19)mm, 5µ. Column flow was 16.0 ml/min. Mobile

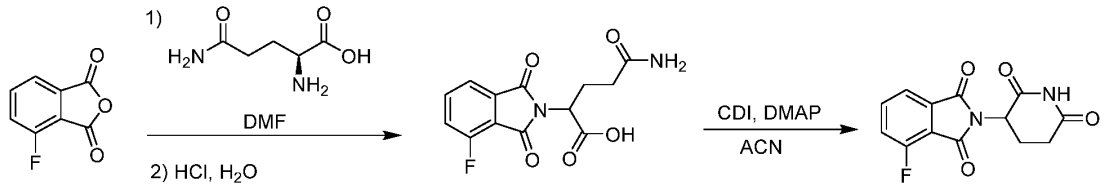
phase used was (A) 0.1% Formic Acid in Water and (B) Acetonitrile. Basic method used was (A) 5mM ammonium bicarbonate and 0.1% NH_3 in Water and (B) Acetonitrile or (A) 0.1% Ammonium Hydroxide in Water and (B) Acetonitrile. The UV spectra were recorded at 202nm & 254nm.

[00518] NMR Method: The 1H NMR spectra were recorded on a Bruker Ultra Shield Advance 400 MHz/5 mm Probe (BBFO). The chemical shifts are reported in part-per-million.

[00519] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

Intermediates

[00520] 2-(2,6-Dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (Intermediate R)



R

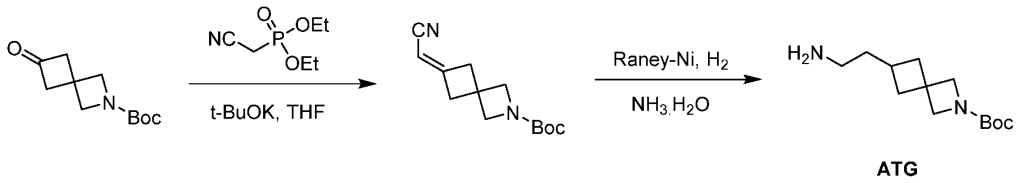
[00521] Step 1 - 5-amino-2-(4-fluoro-1,3-dioxoisoindolin-2-yl)-5-oxopentanoic acid

[00522] To a stirred solution of 4-fluoroisobenzofuran-1,3-dione (25 g, 150 mmol, CAS# 652-39-1) in DMF (100 mL) was added L-glutamine (22 g, 150 mmol) at rt. The resulting reaction mixture was heated to at 90 °C and stirred for 2 h. The reaction mixture was then evaporated under reduced pressure, transferred into 4 N aqueous HCl solution and the resulting mixture was stirred for 36 h at rt. The solid precipitate was then filtered off, washed with cold water and dried under reduced pressure to give 5-amino-2-(4-fluoro-1,3-dioxoisoindolin-2-yl)-5-oxopentanoic acid as a white solid (28 g, 63%). LC-MS (ESI^+) *m/z* 295 $(M+H)^+$.

[00523] Step 2 - 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione

[00524] To a stirred solution of 5-amino-2-(4-fluoro-1,3-dioxoisoindolin-2-yl)-5-oxopentanoic acid (28 g, 95 mmol) in acetonitrile (200 mL) was added CDI (19 g, 110 mmol) and DMAP (0.14 g, 1.1 mmol) at rt. The resulting reaction mixture then heated to 90 °C and stirred for 5 h. The reaction mixture was then evaporated under reduced pressure. The crude product was purified using silica gel column chromatography (2% MeOH-DCM) to give 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione as a yellow solid (12 g, 46%). ^1H NMR (400 MHz, DMSO) δ ppm 11.16 (s, 1H), 7.98-7.93 (m, 1H), 7.80-7.76 (m, 2H), 5.19-5.14 (m, 1H), 2.94-2.85 (m, 1H), 2.63-2.54 (m, 2H), 2.09-2.04 (m, 1H).

[00525] Tert-butyl 6-(2-aminoethyl)-2-azaspiro[3.3]heptane-2-carboxylate (Intermediate ATG)



ATG

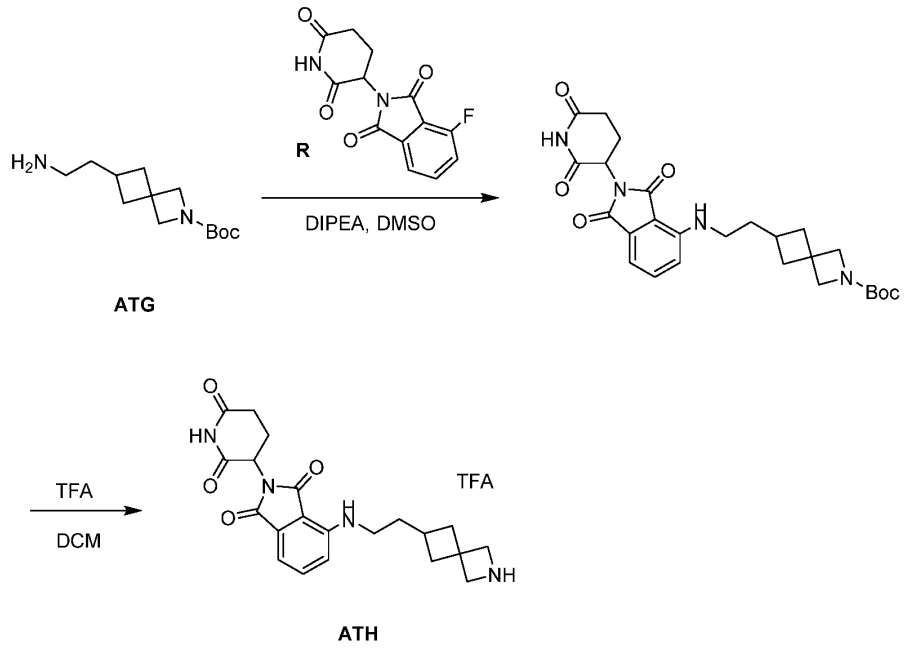
[00526] Step 1 - Tert-butyl 6-(cyanomethylene)-2-azaspiro[3.3]heptane-2-carboxylate

[00527] To a solution of t-BuOK (3.98 g, 35.5 mmol,) in THF (35 mL) was added a solution of 2-diethoxyphosphorylacetonitrile (6.29 g, 35.5 mmol) in THF (70 mL) at 0 °C dropwise, and the reaction was stirred at 25 °C for 0.5 h. After, the mixture was cooled to 0 °C and a solution of tert-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (5.00 g, 23.7 mmol, CAS#1147557-97-8) in THF (35 mL) was added and the reaction was stirred at 25 °C for 16 hours. On completion, the reaction was quenched with water (10 mL) and the solvent was removed *in vacuo* to give a residue. The residue was purified by silica gel column chromatography (PE: EA from 5:1 to 1:1) to give the title compound (4.10 g, 66% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.55 (t, J = 2.4 Hz, 1H), 3.91 (d, J = 2.0 Hz, 4H), 3.17 - 3.01 (m, 4H), 1.37 (s, 9H).

[00528] Step 2 - Tert-butyl 6-(2-aminoethyl)-2-azaspiro[3.3]heptane-2-carboxylate

[00529] To a solution of tert-butyl 6-(cyanomethylene)-2-azaspiro[3.3]heptane-2-carboxylate (4.10 g, 17.5 mmol) in MeOH (80 mL) and $NH_3{\cdot}H_2O$ (8 mL) was added Raney-Ni (1.50 g, 17.5 mmol). The mixture was degassed and purged with H_2 gas 3 times and then was stirred at 25 °C under H_2 at 50 psi for 3 hours. On completion, the reaction was filtered through celite, the filtered cake was washed with MeOH (3 x 5 mL) and the filtrate was concentrated *in vacuo* to give the title compound (3.10 g, 66% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (d, J = 7.6 Hz, 4H), 2.47 - 2.00 (m, 5H), 1.79 - 1.67 (m, 2H), 1.46 - 1.38 (m, 2H), 1.36 (s, 9H).

[00530] 4-[2-(2-Azaspiro[3.3]heptan-6-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (Intermediate ATH)



ATH

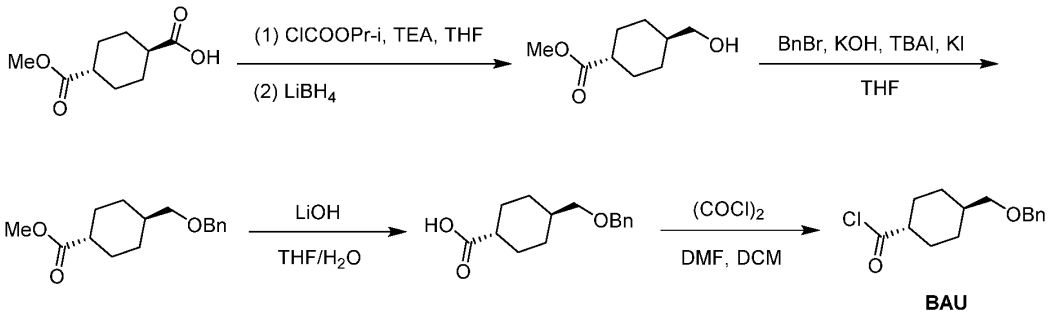
[00531] Step 1 - Tert-butyl 6-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]-2-azaspiro [3.3]heptane-2-carboxylate

[00532] To a solution of tert-butyl 6-(2-aminoethyl)-2-azaspiro[3.3]heptane-2-carboxylate (3.00 g, 12.5 mmol, Intermediate ATG) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (3.79 g, 13.7 mmol, Intermediate R) in DMSO (30 mL) was added DIPEA (4.84 g, 37.5 mmol). The mixture was stirred at 130 °C for 1 hour. On completion, the reaction was diluted with EA (150 mL), washed with water (3 X 50 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude product which was purified by reversed phase (0.1% FA condition) to give the title compound (3.20 g, 46% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 7.59 (dd, J = 7.2, 8.4 Hz, 1H), 7.11 - 6.97 (m, 2H), 6.49 (t, J = 5.6 Hz, 1H), 5.06 (dd, J = 5.6, 12.8 Hz, 1H), 3.84 (s, 2H), 3.73 (s, 2H), 3.22 (q, J = 6.4 Hz, 2H), 2.91 - 2.83 (m, 1H), 2.65 - 2.54 (m, 2H), 2.32 - 2.22 (m, 2H), 2.16 (t, J = 7.6 Hz, 1H), 2.04 (d, J = 2.4 Hz, 1H), 1.86 - 1.78 (m, 2H), 1.65 (q, J = 7.2 Hz, 2H), 1.36 (s, 9H); LC-MS (ESI$^+$) m/z 497.3 $(M+H)^+$.

[00533] Step 2 - 4-[2-(2-Azaspiro[3.3]heptan-6-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione

[00534] To a solution of tert-butyl 6-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (0.30 g, 604 umol) in DCM (3 mL) was added TFA (2.31 g, 20.3 mmol). The mixture was stirred at 25 °C for 1 hour. On completion, the reaction was concentrated *in vacuo* to give the title compound (0.18 g, TFA, 58% yield) as a yellow solid.

[00535] (1R,4r)-4-((Benzyloxy)methyl)cyclohexanecarbonyl chloride (Intermediate BAU)



[00536] Step 1 - (1R,4r)-Methyl 4-(hydroxymethyl)cyclohexanecarboxylate

[00537] To a solution of 4-methoxycarbonylcyclohexanecarboxylic acid (20.0 g, 107 mmol, CAS# 15177-67-0) in the THF (200 mL) was added Et_3N (21.7 g, 215 mmol, 29.9 mL) and isopropyl carbonochloridate (19.7 g, 161 mmol, 22.4 mL) at 0 °C. The mixture was stirred at 25 °C for 1 hour. Then the mixture was filtered and the $LiBH_4$ (11.7 g, 537 mmol) was added in portion at 0 °C. The mixture was stirred at 25 °C for 4 hours. On completion, the mixture was quenched by water (500 mL) and extracted with EA (3 X 1000 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (9.70 g, 52% yield) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.47 (d, J = 6.0 Hz, 2H), 2.26 (tt, J = 3.6, 12.4 Hz, 1H), 2.06 - 1.99 (m, 2H), 1.88 (dd, J = 3.2, 13.6 Hz, 2H), 1.56 - 1.39 (m, 3H), 1.07 - 0.93 (m, 2H).

[00538] Step 2 - (1R,4r)-Methyl 4-((benzyloxy)methyl)cyclohexanecarboxylate

[00539] To a solution of methyl 4-(hydroxymethyl)cyclohexanecarboxylate (9.70 g, 56.3 mmol) in the THF (100 mL) was added KOH (4.74 g, 84.5 mmol), TBAI (4.16 g, 11.3 mmol), KI (1.87 g, 11.3 mmol) and BnBr (14.5 g, 84.5 mmol, 10.0 mL). The mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (11.0 g, 74% yield) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.27 (m, 5H), 4.50 (s, 2H), 3.67 (s, 3H), 3.29 (d, J = 6.4 Hz, 2H), 2.25 (tt, J = 3.6, 12.4 Hz, 1H), 2.04 - 1.98 (m, 2H), 1.91 (br dd, J = 3.6, 13.6 Hz, 2H), 1.71 - 1.61 (m, 1H), 1.45 - 1.42 (m, 2H), 1.08 - 0.94 (m, 2H).

[00540] Step 3 - (1R,4r)-4-((benzyloxy)methyl)cyclohexanecarboxylic acid

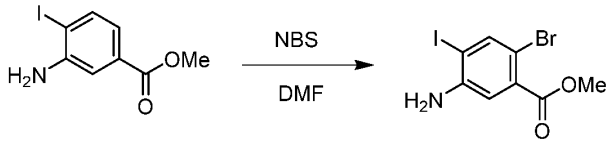
[00541] To a solution of methyl 4-(benzyloxymethyl)cyclohexanecarboxylate (11.0 g, 41.9 mmol) in the THF (100 mL), MeOH (20 mL) and H_2O (20 mL) was added LiOH (5.02 g, 210 mmol). The mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was diluted with water (100 mL) and washed with PE (200 mL). The water phase was acidifed by HCl (aq, 1M) to pH = 4. Then the mixture was extracted with DCM (3 X 200 mL). The organic layer was

dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (10.1 g, 97% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.26 (m, 5H), 4.50 (s, 2H), 3.30 (d, *J* = 6.4 Hz, 2H), 2.28 (tt, *J* = 3.6, 12.4 Hz, 1H), 2.05 (dd, *J* = 2.8, 13.6 Hz, 2H), 1.92 (dd, *J* = 2.8, 13.6 Hz, 2H), 1.65 - 1.62 (m, 1H), 1.46 (dq, *J* = 3.6, 12.8 Hz, 2H), 1.11 - 0.95 (m, 2H).

[00542] Step 4 - (1R,4r)-4-((Benzyloxy)methyl)cyclohexanecarbonyl chloride

[00543] To a solution of 4-(benzyloxymethyl)cyclohexanecarboxylic acid (10.0 g, 40.3 mmol) in the DCM (100 mL) was added DMF (294 mg, 4.03 mmol) and $(COCl)_2$ (7.67 g, 60.4 mmol, 5.29 mL) in portion at 0 °C. The mixture was stirred at 0 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (10.7 g, 99% yield) as yellow oil.

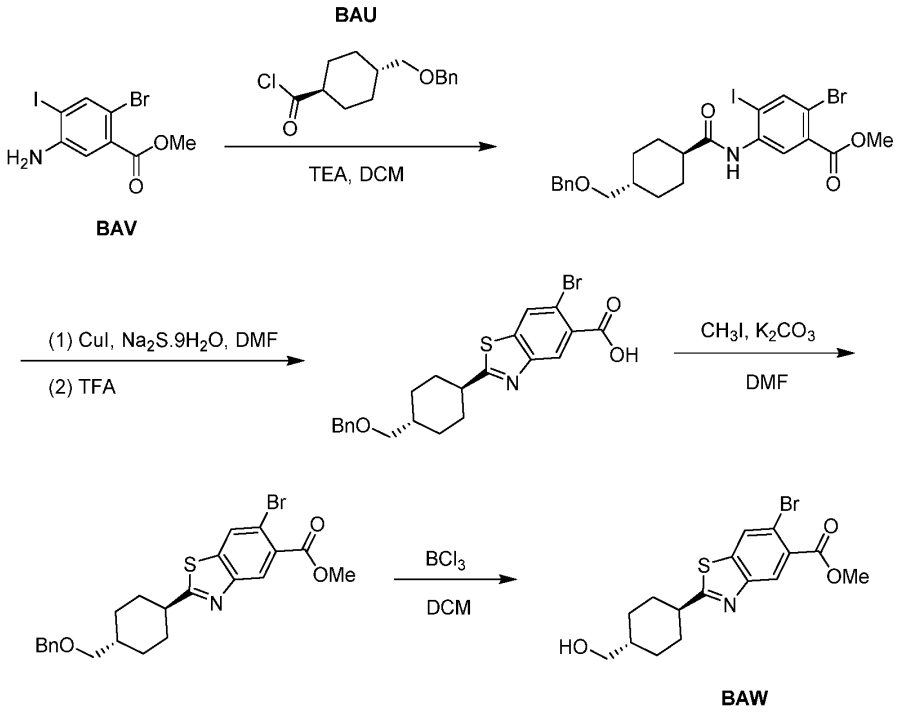
[00544] Methyl 5-amino-2-bromo-4-iodo-benzoate (Intermediate BAV)



BAV

[00545] To a solution of methyl 3-amino-4-iodo-benzoate (5.00 g, 18.1 mmol, CAS# 412947-54-7) in DMF (25 mL) was added NBS (3.28 g, 18.4 mmol). The mixture was stirred at 0 °C for 2 hours. On completion, the mixture was poured into 500 mL water and a solid was obtained. The mixture was filtered then the filtered cake was washed with water (3 X 50 mL) and dried *in vacuo* to give the title compound (6.00 g, 93% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.13 (s, 1H), 5.66 (br s, 2H), 3.81 (s, 3H).

[00546] Methyl 6-bromo-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazole-5-carboxylate (Intermediate BAW)



[00547] Step 1 - Methyl 5-[[4-(benzyloxymethyl)cyclohexanecarbonyl]amino]-2-bromo-4-iodo-benzoate

[00548] To a solution of methyl 5-amino-2-bromo-4-iodo-benzoate (707 mg, 1.9 mmol, Intermediate BAV) in DCM (10 mL) was added Et_3N (603 mg, 5.96 mmol). Then a mixture of 4-(benzyloxymethyl)cyclohexane carbonyl chloride (530 mg, 1.99 mmol, Intermediate BAU) in DCM (20 mL) was added to the reaction mixture. The mixture was stirred at 0 °C for 2 hours. On completion, the mixture was concentrated *in vacuo*. The residue was diluted with water (50 mL) and extracted with EA (3 X 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated of most solvent. Then the solid was precipitated out, then filtered, the cake was dried *in vacuo* to give the title compound (660 mg, 56% yield) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 1.6 Hz, 1H), 8.09 (d, J = 1.6 Hz, 1H), 7.52 (s, 1H), 7.41 - 7.27 (m, 5H), 4.52 (d, J = 1.6 Hz, 2H), 3.92 (d, J = 1.6 Hz, 3H), 3.34 (dd, J = 1.6, 6.0 Hz, 2H), 2.35 - 2.24 (m, 1H), 2.12 (d, J = 13.2 Hz, 2H), 2.00 (d, J = 13.2 Hz, 2H), 1.77 - 1.58 (m, 3H), 1.19 - 1.05 (m, 2H).

[00549] Step 2 - 2-[4-(Benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylic acid

[00550] To a solution of methyl 5-[[4-(benzyloxymethyl)cyclohexanecarbonyl]amino]-2-bromo-4-iodo- benzoate (5.60 g, 9.55 mmol) in DMF (50 mL) was added CuI (363 mg, 1.91 mmol) and $Na_2S{\cdot}9H_2O$ (13.7 g, 57.3 mmol). The mixture was stirred at 80 °C for 6 hours, and then cooled to rt. Then TFA (15.4 g,

135 mmol) was added to the mixture and the mixture was stirred at 25 °C for 6 hours. On completion, the residue was diluted with water (100 mL) and extracted with EA (3 X 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (4.00 g, 56% yield) as yellow oil. LC-MS (ESI+) m/z 462.1 $(M+3)^+$.

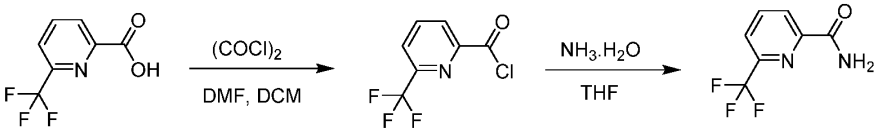
[00551] Step 3 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate

[00552] To a solution of 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylic acid (4.00 g, 8.69 mmol) in DMF (20 mL) was added CH_3I (2.47 g, 17.3 mmol) and K_2CO_3 (2.40 g, 17.3 mmol). The mixture was stirred at 15 °C for 2 hours. On completion, the mixture was filtered and concentrated *in vacuo*. The residue was purified by flash silica gel chromatography (PE: EA 3:1) to give title compound (3.00 g, 72% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.05 (s, 1H), 7.31 - 7.21 (m, 5H), 4.44 (s, 2H), 3.88 (s, 3H), 3.27 (d, J = 6.0 Hz, 2H), 2.97 (t, J = 12.0 Hz, 1H), 2.87 (s, 5H), 2.80 (s, 5H), 2.19 (d, J = 12.4 Hz, 2H), 1.95 (d, J = 13.6 Hz, 2H), 1.73 - 1.65 (m, 1H), 1.58 (q, J = 12.8 Hz, 2H), 1.20 - 1.07 (m, 2H).

[00553] Step 4 - Methyl 6-bromo-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazole-5-carboxylate

[00554] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate (2.00 g, 4.22 mmol) in DCM (40 mL) was added BCl_3 (9.88 g, 84.3 mmol). The mixture was stirred at 25 °C for 2 hours. On completion, to the mixture was added sat.$NaHCO_3$. aq (50 mL) then extracted with DCM (3 X 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.60 g, 90% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.21 - 8.13 (m, 1H), 3.98 (s, 3H), 3.55 (d, J = 6.0 Hz, 2H), 3.25 - 3.12 (m, 1H), 2.42 - 2.26 (m, 2H), 2.09 - 1.98 (m, 2H), 1.78 - 1.62 (m, 3H), 1.29 - 1.16 (m, 2H).

[00555] 6-(Trifluoromethyl)pyridine-2-carboxamide (Intermediate ATI)



ATI

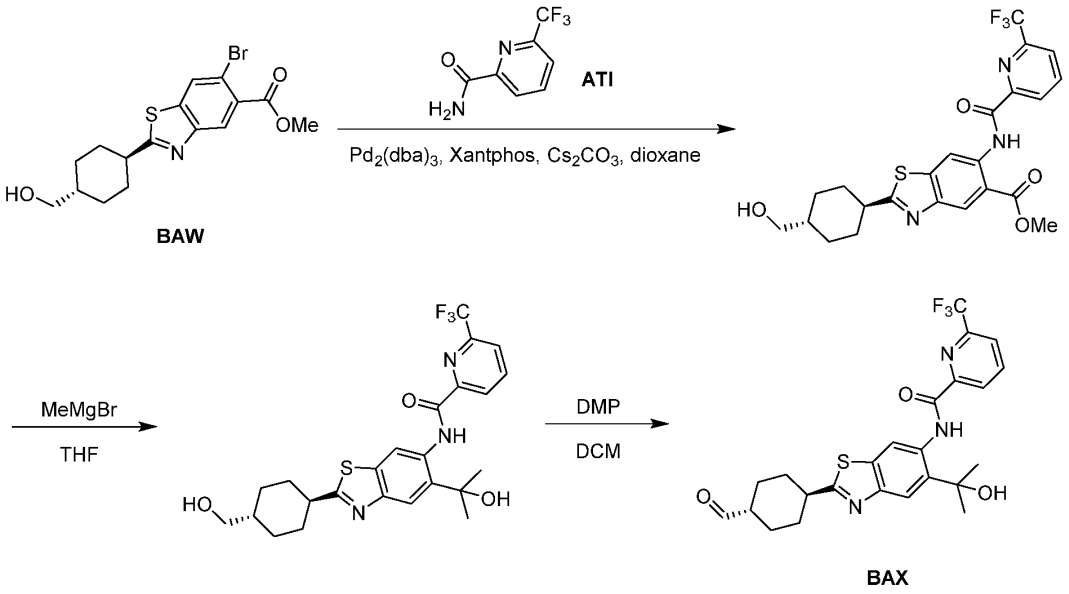
[00556] Step 1 - 6-(Trifluoromethyl)pyridine-2-carbonyl chloride

[00557] To a mixture of 6-(trifluoromethyl)pyridine-2-carboxylic acid (21.0 g, 109 mmol, CAS# 131747-42-7) and DMF (401 mg, 5.49 mmol) in DCM (300 mL) was added $(COCl)_2$ (27.9 g, 219 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (22 g, 95% yield) as light yellow oil.

[00558] Step 2 - 6-(Trifluoromethyl)pyridine-2-carboxamide

[00559] A solution of 6-(trifluoromethyl)pyridine-2-carbonyl chloride (21.5 g, 102 mmol) in THF (100 mL) was added $NH_3 \cdot H_2O$ (143 g, 1.03 mol, 158 mL, 25% solution) at 0 °C. The mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo* to remove THF and then filtered to give the filter cake as title product (19 g, 90% yield) as light yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.35 - 8.24 (m, 2H), 8.08 (dd, J = 1.6, 6.8 Hz, 1H), 8.05 - 7.78 (m, 2H); LC-MS (ESI$^+$) m/z 191.0 $(M+H)^+$.

[00560] N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BAX)



[00561] Step 1 - Methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino] -1,3-benzothiazole-5-carboxylate

[00562] To a solution of methyl 6-bromo-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazole-5-carboxylate (300 mg, 780 umol, Intermediate BAW) and 6-(trifluoromethyl)pyridine-2-carboxamide (163 mg, 858 umol, Intermediate ATI) in dioxane (30 mL) was added Xantphos (90.3 mg, 156 umol), Cs_2CO_3 (763 mg, 2.34 mmol) and $Pd_2(dba)_3$ (71.4 mg, 78.1 umol) at 25 °C. The mixture was stirred at 80 °C for 12 hrs under N_2. On completion, the mixture was filtered with celite and concentrated *in vacuo*. The residue was purified by column chromatography to give title compound (120 mg, 31% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 9.44 (s, 1H), 8.54 (s, 1H), 8.50 - 8.46 (m, 1H), 8.45 - 8.38 (m, 1H), 8.23 (d, J = 7.8 Hz, 1H), 4.53 - 4.40 (m, 1H), 3.98 (s, 3H), 3.27 (t, J = 5.6 Hz, 2H), 3.08 (s, 1H), 2.19 (d, J = 13.0 Hz, 2H), 1.93 - 1.83 (m, 2H), 1.66 - 1.51 (m, 2H), 1.48 - 1.38 (m, 1H), 1.18 - 1.05 (m, 2H).

[00563] Step 2 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-

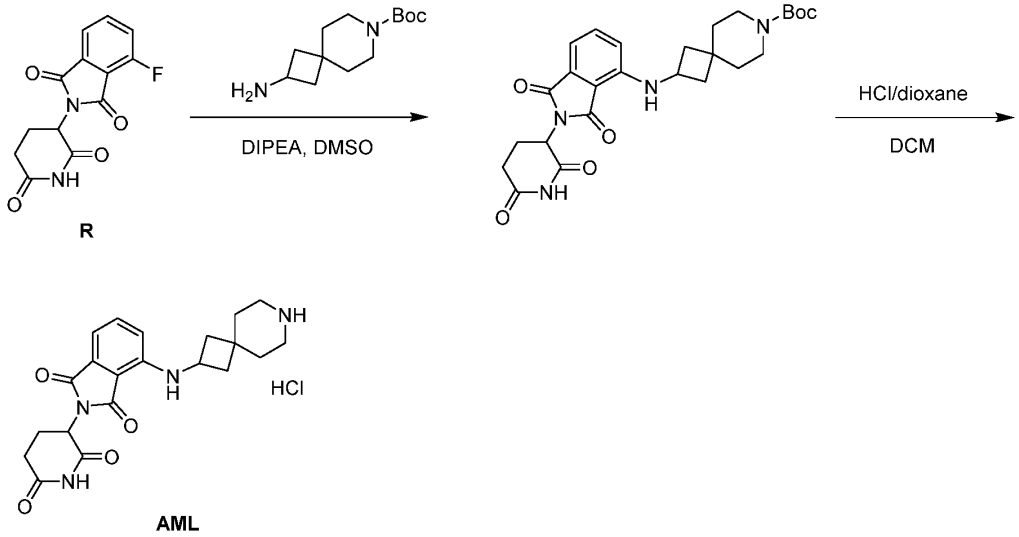
benzothiazol-6-yl] -6-(trifluoromethyl)pyridine-2-carboxamide

[00564] To a solution of methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-[[6-(trifluoromethyl)pyridine-2-carbonyl] amino]-1,3-benzothiazole-5-carboxylate (120 mg, 243 umol) in THF (10 mL) was added MeMgBr (3 M, 405 uL). The mixture was stirred at 0 °C for 2 hours. The reaction mixture was quenched by addition sat. NH_4Cl (10 mL) at 0 °C, and then diluted with water (50 mL) and extracted with EA (3 X 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 um; mobile phase: [water (0.225%FA)-ACN]; B%: 44%-74%, 10 min) to give the title compound (80.0 mg, 60% yield) as white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 9.07 (s, 1H), 8.51 - 8.45 (m, 1H), 8.39 (t, J = 8.0 Hz, 1H), 8.20 (d, J = 7.6 Hz, 1H), 7.94 - 7.88 (m, 1H), 6.08 (s, 1H), 4.46 (t, J = 5.2 Hz, 1H), 3.28 (t, J = 5.6 Hz, 2H), 3.10 - 3.00 (m, 1H), 2.19 (d, J = 11.2 Hz, 2H), 1.94 - 1.84 (m, 2H), 1.64 (s, 6H), 1.61 - 1.53 (m, 2H), 1.50 - 1.40 (m, 1H), 1.19 - 1.06 (m, 2H).

[00565] Step 3 - N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

[00566] To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol -6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (50.0 mg, 101 umol) in DCM (10 mL) was added DMP (51.5 mg, 121 umol). The mixture was stirred at 25 °C for 2 hours. On completion, the mixture was added 10 mL sat. $NaHCO_3$ and 10 mL sat. $Na_2S_2O_3$, then extracted with DCM (3 X 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (60.0 mg, 90 % yield) as yellow solid. LC-MS (ESI^+) m/z 492.2 $(M+1)^+$.

[00567] 4-(7-Azaspiro[3.5]nonan-2-ylamino)-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (Intermediate AML)



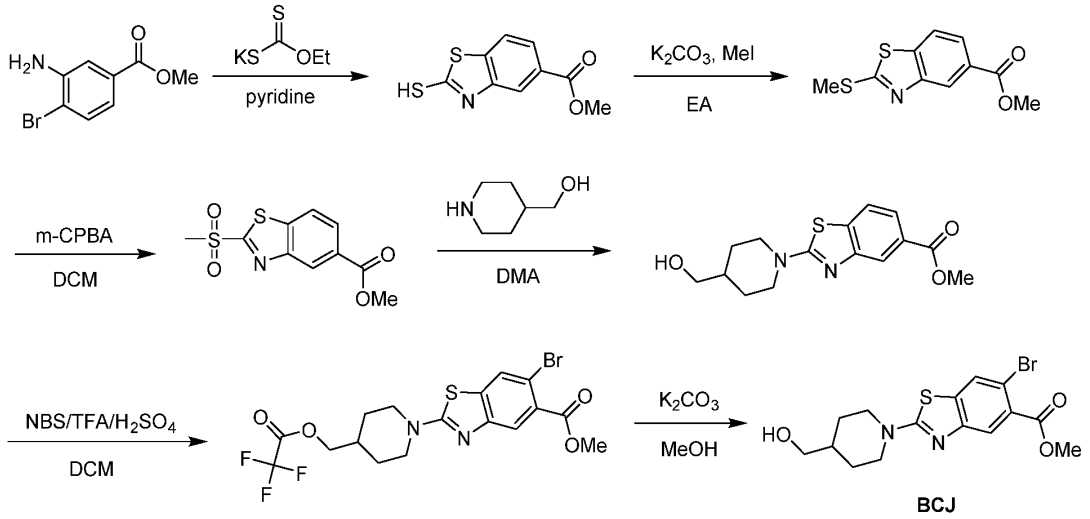
[00568] Step 1 - Tert-butyl 2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]-7-azaspiro[3.5] nonane-7-carboxylate

[00569] To a mixture of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (0.50 g, 1.81 mmol, Intermediate R) and tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate (478 mg, 1.99 mmol, CAS# 1239319-82-4) in DMSO (10 mL) was added DIPEA (468 mg, 3.62 mmol). The mixture was stirred at 130 °C for 2 hours. On completion, the reaction mixture was poured into the water (30 mL), and extracted with EA (2 X 20 mL). The combined organic phase was washed with brine (2 X 30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (0.80 g, 89% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.11 (d, J = 7.2 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 5.6 Hz, 1H), 4.95 - 4.89 (m, 1H), 4.08 - 3.99 (m, 1H), 3.42 - 3.35 (m, 2H), 3.33 - 3.26 (m, 2H), 2.93 - 2.84 (m, 1H), 2.83 - 2.71 (m, 2H), 2.48 - 2.35 (m, 2H), 2.17 - 2.09 (m, 1H), 1.78 - 1.71 (m, 2H), 1.65 - 1.60 (m, 2H), 1.58 - 1.52 (m, 2H), 1.45 (s, 9H).

[00570] Step 2 - 4-(7-Azaspiro[3.5]nonan-2-ylamino)-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione

[00571] To a mixture of tert-butyl 2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]-7 - azaspiro[3.5]nonane-7-carboxylate (0.80 g, 1.61 mmol) in DCM (20 mL) was added HCl/dioxane (4 M, 1.21 mL). The reaction mixture was stirred at 20 °C for 0.5 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (690 mg, 98% yield) as a yellow solid. LC-MS (ESI^+) *m/z* 397.2 $(M+H)^+$.

[00572] Methyl 6-bromo-2-[4-(hydroxymethyl)-1-piperidyl]-1,3-benzothiazole-5-carboxylate (Intermediate BCJ)



BCJ

[00573] Step 1 - Methyl 2-sulfanyl-1,3-benzothiazole-5-carboxylate

[00574] To a solution of methyl 3-amino-4-bromo-benzoate (5.00 g, 21.7 mmol, CAS# 46064-79-3) in pyridine (60 mL) was added ethoxycarbothioylsulfanylpotassium (5.23 g, 32.6 mmol) at 25 °C. The reaction mixture was stirred at 110 °C for 12 hours under N_2. On completion, the reaction mixture was concentrated *in vacuo* to remove pyridine, then the mixture was redissolved with 50 mL H_2O and aq 1N HCl was added to adjust pH = 1-2. The above mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound (4.00 g, 65% yield, 80% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.98 (s, 1H), 7.84 (s, 2H), 7.80 (s, 1H), 3.88 (s, 3H).

[00575] Step 2 - Methyl 2-methylsulfanyl-1,3-benzothiazole-5-carboxylate

[00576] To a solution of methyl 2-sulfanyl-1,3-benzothiazole-5-carboxylate (3.80 g, 16.8 mmol) and K_2CO_3 (245 mg, 1.78 mmol) in EA (50 mL) was added CH_3I (33.7 mmol, 2.10 mL). The mixture was stirred at 25 °C for 2 hours. On completion, the mixture was filtered and washed with EA (3 X 50 mL). The organic phase was concentrated *in vacuo* and the residue was purified by flash silica gel chromatography (PE:EA = 5:1) to give the title compound (3.00 g, 74% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 0.8 Hz, 1H), 7.98 (dd, J = 1.6, 8.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 3.97 (s, 3H), 2.82 (s, 3H); LC-MS (ESI$^+$) m/z 240.2 $(M+H)^+$.

[00577] Step 3 - Methyl 2-methylsulfonyl-1,3-benzothiazole-5-carboxylate

[00578] To a solution of methyl 2-methylsulfanyl-1,3-benzothiazole-5-carboxylate (2.00 g, 8.36 mmol) in DCM (20 mL) was added m-CPBA (1.87 g, 10.8 mmol). The mixture was stirred at 25 °C for 6 hours. On completion, to the mixture was added sat. $NaHCO_3$. (20 mL) and sat. $Na_2S_2O_3$ (20 mL), then the mixture was extracted with DCM 90 mL (3 X 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give the title compound (2.20

g, 97% yield) as a white solid. LC-MS (ESI^+) m/z 272.0 $(M+H)^+$.

[00579] Step 4 - Methyl 2-[4-(hydroxymethyl)-1-piperidyl]-1,3-benzothiazole-5-carboxylate

[00580] To a solution of methyl 2-methylsulfonyl-1,3-benzothiazole-5-carboxylate (1.10 g, 4.05 mmol) and 4-piperidylmethanol (933 mg, 8.11 mmol, CAS# 6457-49-4) in DMA (10 mL). The mixture was stirred at 130 °C for 0.5 hr under microwave irradiation. On completion, the reaction mixture was diluted with 100 mL water and extracted with EA 150 mL (3 X 50 mL). The combined organic layers were washed with 100 mL brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.30 g, crude) as white solid. LC-MS (ESI^+) m/z 307.1 $(M+H)^+$.

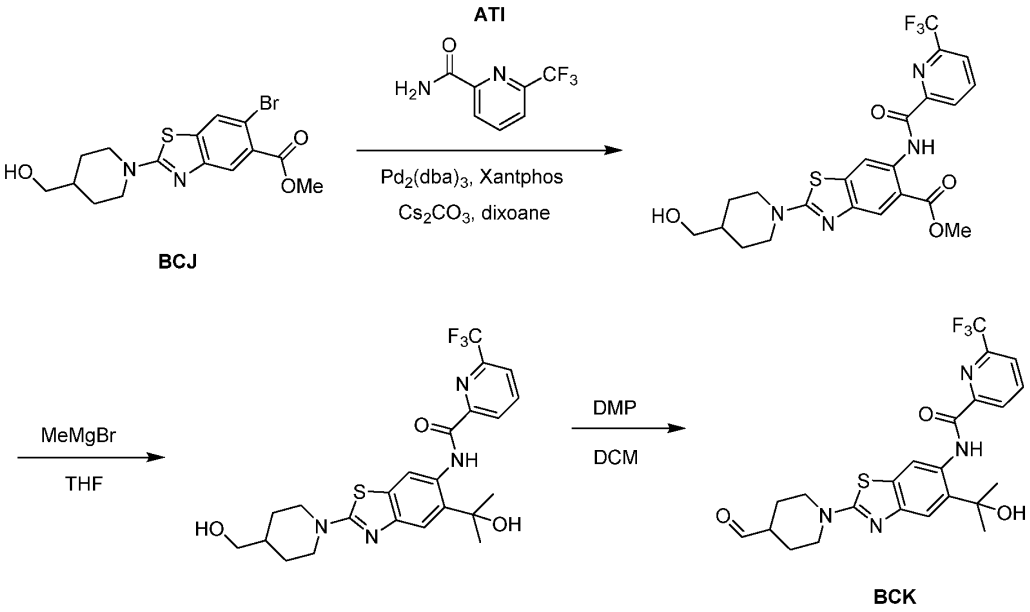
[00581] Step 5 - Methyl 6-bromo-2-[4-[(2,2,2-trifluoroacetyl)oxymethyl]-1-piperidyl]-1,3-benzothiazole-5- carboxylate

[00582] To a solution of methyl 2-[4-(hydroxymethyl)-1-piperidyl]-1,3-benzothiazole-5-carboxylate (1.20 g, 3.92 mmol) in TFA (10 mL) and H_2SO_4 (5 mL) and DCM (10 mL) was added NBS (906 mg, 5.09 mmol). The mixture was stirred at 0 °C for 2 hrs. On completion, the reaction mixture was diluted with 50 mL ice water and extracted with DCM 150 mL (3 X 50 mL). The combined organic layers were washed with 100 mL brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (2.00 g, crude) as yellow oil. LC-MS (ESI^+) m/z 482.8 $(M+3)^+$.

[00583] Step 6 - Methyl 6-bromo-2-[4-(hydroxymethyl)-1-piperidyl]-1,3-benzothiazole-5-carboxylate

[00584] To a solution of methyl 6-bromo-2-[4-[(2,2,2-trifluoroacetyl)oxymethyl]-1-piperidyl]-1,3-benzothiazole-5-carboxylate (2.00 g, 4.16 mmol) in MeOH (60 mL) was added K_2CO_3 (1.72 g, 12.4 mmol). The mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue phase was purified by reverse phase (0.1 % FA condition) to give the title compound (400 mg, 24% yield) as yellow solid. LC-MS (ESI^+) m/z 387.0 $(M+3)^+$.

[00585] N-[2-(4-formyl-1-piperidyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BCK)



[00586] Step 1 - Methyl 2-[4-(hydroxymethyl)-1-piperidyl]-6-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino] -1,3-benzothiazole-5-carboxylate

[00587] To a solution of methyl 6-bromo-2-[4-(hydroxymethyl)-1-piperidyl]-1,3-benzothiazole-5-carboxylate (350 mg, 908 umol, Intermediate BCJ) and 6-(trifluoromethyl)pyridine-2-carboxamide (172 mg, 908 umol, Intermediate ATI) in dioxane (20 mL) was added $Pd_2(dba)_3$ (83.1 mg, 90.8 umol), Xantphos (105 mg, 181 umol) and Cs_2CO_3 (591 mg, 1.82 mmol) at 25 °C. The reaction mixture was stirred at 80 °C for 12 hours under N_2. On completion, the reaction mixture was filtered, and then the residue was diluted with 50 mL water and extracted with EA 150 mL (3 X 50 mL). The combined organic layers were washed with 100 mL brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue phase was purified by flash silica gel chromatography (PE: EA = 1:1) to give the title compound (250 mg, 55% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (s, 1H), 9.20 (s, 1H), 8.50 - 8.45 (m, 1H), 8.44 - 8.38 (m, 1H), 8.23 (dd, J = 0.8, 8.4 Hz, 1H), 8.03 (s, 1H), 4.56 (t, J = 5.6 Hz, 1H), 4.11 - 4.04 (m, 2H), 3.95 (s, 3H), 3.29 (s, 2H), 3.24 - 3.14 (m, 2H), 1.86 - 1.76 (m, 2H), 1.74 - 1.64 (m, 1H), 1.30 - 1.21 (m, 2H); LC-MS (ESI$^+$) m/z 495.1 $(M+H)^+$.

[00588] Step 2 - N-[5-(1-Hydroxy-1-methyl-ethyl)-2-[4-(hydroxymethyl)-1-piperidyl]-1,3-benzothiazol-6-yl] -6-(trifluoromethyl)pyridine-2-carboxamide

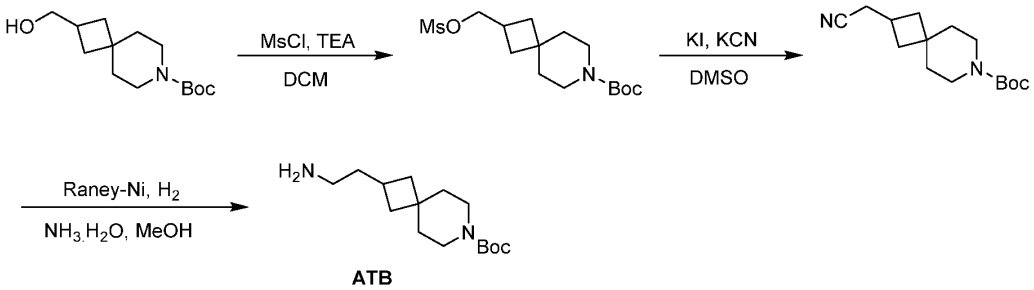
[00589] To a solution of methyl 2-[4-(hydroxymethyl)-1-piperidyl]-6-[[6-(trifluoromethyl)pyridine-2-carbonyl] amino]-1,3-benzothiazole-5-carboxylate (200 mg, 404 umol) in THF (10 mL) was added MeMgBr (3 M, 674 uL). The mixture was stirred at 0 °C for 2 hours. On completion, the reaction mixture

was quenched with 10 mL sat. NH_4Cl. Then the mixture was diluted with 50 mL water and extracted with EA 90 mL (3 X 30 mL). The combined organic layers were washed with 50 mL brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (250 mg, 80% purity, 100% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 8.79 (s, 1H), 8.49 - 8.43 (m, 1H), 8.41 - 8.34 (m, 1H), 8.17 (dd, J = 0.8, 8.4 Hz, 1H), 7.43 (s, 1H), 5.96 (s, 1H), 4.55 (t, J = 5.2 Hz, 1H), 4.10 - 4.00 (m, 2H), 3.31 - 3.27 (m, 2H), 3.20 - 3.10 (m, 2H), 1.79 (d, J = 12.8 Hz, 3H), 1.73 - 1.65 (m, 1H), 1.59 (s, 6H), 1.29 - 1.21 (m, 2H); LC-MS (ESI^+) m/z 495.2 $(M+H)^+$.

[00590] Step 3 - N-[2-(4-formyl-1-piperidyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

[00591] To a solution of N-[5-(1-hydroxy-1-methyl-ethyl)-2-[4-(hydroxymethyl)-1-piperidyl]-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (240 mg, 485 umol) in DCM (2 mL) was added DMP (71.1 mg, 582 umol). The mixture was stirred at 15 °C for 2 hours. On completion, the reaction mixture was added 10 mL sat. $NaHCO_3$ aq and 10 mL sat. $Na_2S_2O_3$ aq, and then the mixture was extracted with DCM 90 mL (3 X 30 mL). The combined organic layers were washed with 50 mL brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (150 mg, 63% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 9.64 (s, 1H), 8.88 - 8.73 (m, 1H), 8.48 - 8.42 (m, 1H), 8.41 - 8.35 (m, 1H), 8.21 - 8.14 (m, 1H), 7.47 - 7.41 (m, 1H), 6.04 - 5.88 (m, 1H), 4.08 - 4.00 (m, 1H), 3.99 - 3.91 (m, 1H), 3.31 (s, 4H), 3.24 - 3.04 (m, 1H), 2.08 - 1.94 (m, 1H), 1.89 - 1.74 (m, 1H), 1.59 (s, 6H), 1.40 - 1.14 (m, 1H); LC-MS (ESI^+) m/z 493.1 $(M+H)^+$.

[00592] Tert-butyl 2-(2-aminoethyl)-7-azaspiro[3.5]nonane-7-carboxylate (Intermediate ATB)



ATB

[00593] Step 1 - Tert-butyl 2-(methylsulfonyloxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate

[00594] To a solution of tert-butyl 2-(hydroxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (1.00 g, 3.92 mmol, CAS# 1356476-27-1) and TEA (594 mg, 5.87 mmol) in DCM (15 mL) was added MsCl (538 mg, 4.70 mmol) at 0 °C. The reaction mixture was stirred at 0~ 20 °C for 1 hr. On completion, the reaction mixture was diluted with water (30 mL) and extracted with DCM (3 X 40 mL). The combined organic layers were washed with brine (2 X 30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give

the title compound (1.20 g, 91% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (d, J = 6.4 Hz, 2H), 3.41 - 3.32 (m, 2H), 3.30 - 3.23 (m, 2H), 3.02 (s, 3H), 2.75 - 2.62 (m, 1H), 2.03 - 1.93 (m, 2H), 1.66 - 1.61 (m, 2H), 1.61 -1.59 (m, 1H), 1.58 - 1.56 (m, 1H), 1.50 - 1.47 (m, 2H), 1.45 (s, 9H).

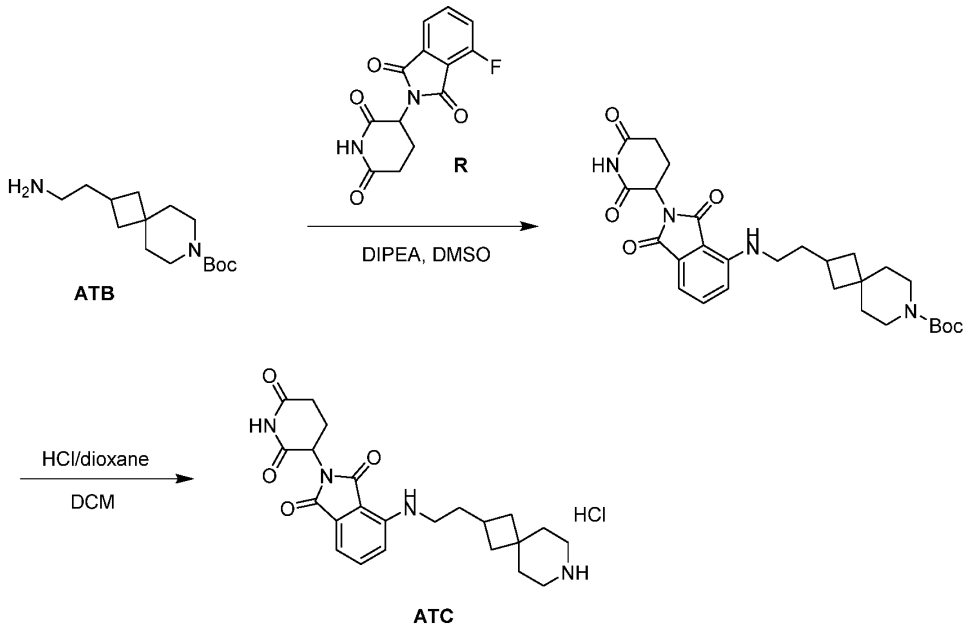
[00595] Step 2 - Tert-butyl 2-(cyanomethyl)-7-azaspiro[3.5]nonane-7-carboxylate

[00596] To a solution of tert-butyl 2-(methylsulfonyloxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (1.20 g, 3.60 mmol) and KI (896 mg, 5.40 mmol) in DMSO (15 mL) was added KCN (257 mg, 3.96 mmol,) at 25 °C. The reaction mixture was stirred at 100 °C for 4 hrs. On completion, the reaction mixture was diluted with water (100 mL) and extracted with EA (3 X 60 mL). The combined organic layers were washed with brine (2 X 30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 10: 1) to give the title compound (510 mg, 53% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 - 3.33 (m, 2H), 3.31 - 3.22 (m, 2H), 2.70 - 2.52 (m, 1H), 2.45 (d, J = 6.4 Hz, 2H), 2.14 - 1.99 (m, 2H), 1.68 - 1.58 (m, 4H), 1.54 - 1.48 (m, 2H), 1.46 (s, 9H).

[00597] Step 3 - Tert-butyl 2-(2-aminoethyl)-7-azaspiro[3.5]nonane-7-carboxylate

[00598] To a solution of tert-butyl 2-(cyanomethyl)-7-azaspiro[3.5]nonane-7-carboxylate (0.50 g, 1.89 mmol) and NH_3•H_2O (910 mg, 7.27 mmol, 28% solution) in MeOH (10 mL) was added Raney-Ni (32.4 mg, 378 umol). The reaction mixture was stirred at 20 °C for 3 hrs under hydrogen (50 psi). On completion, the reaction mixture was filtered and the filter cake was washed with methanol (50 mL). The combined organic phase was concentrated *in vacuo* to give the title compound (400 mg, 78 % yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.25 - 3.23 (m, 2H), 3.17 - 3.14 (m, 2H), 2.42 (t, J = 7.2 Hz, 2H), 2.30 - 2.17 (m, 1H), 1.93 - 1.84 (m, 2H), 1.49 - 1.41 (m, 4H), 1.37 (s, 9H), 1.36 - 1.28 (m, 4H).

[00599] 4-[2-(7-Azaspiro[3.5]nonan-2-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (Intermediate ATC)



[00600] Step 1 - Tert-butyl 2-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]-7-azaspiro [3.5]nonane-7-carboxylate

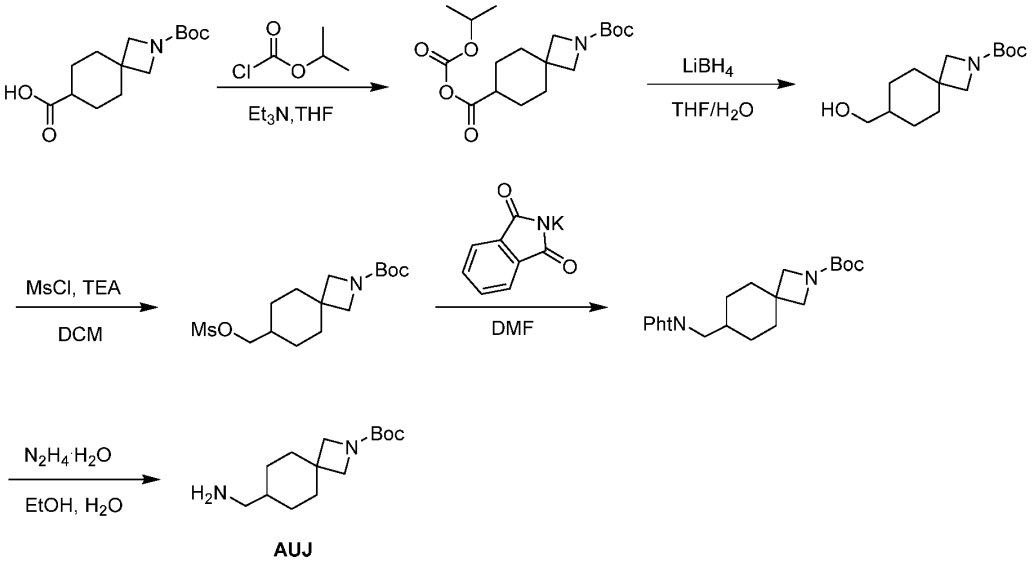
[00601] To a solution of tert-butyl 2-(2-aminoethyl)-7-azaspiro[3.5]nonane-7-carboxylate (160 mg, 596 umol, Intermediate ATB) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (181 mg, 655 umol, Intermediate R) in DMSO (3 mL) was added DIPEA (154 mg, 1.19 mmol). The reaction mixture was stirred at 130 °C for 2 hrs. On completion, the reaction mixture was diluted with water (10 mL) and extracted with EA (3 X 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase (0.1% FA) to give the title compound (200 mg, 63% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 7.58 (dd, J = 7.2, 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 6.8 Hz, 1H), 6.47 (t, J = 5.6 Hz, 1H), 5.04 (dd, J = 5.2, 12.8 Hz, 1H), 3.28 -3.24 (m, 2H), 3.24 - 3.20 (m, 2H), 3.19 -3.14 (m, 2H), 2.93 - 2.80 (m, 1H), 2.63 - 2.54 (m, 2H), 2.31 - 2.22 (m, 1H), 2.07 - 1.99 (m, 1H), 1.98 - 1.90 (m, 2H), 1.74 - 1.64 (m, 2H), 1.51 - 1.38 (m, 6H), 1.37 (s, 9H).

[00602] Step 2 - 4-[2-(7-Azaspiro[3.5]nonan-2-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione

[00603] To a solution of tert-butyl 2-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]-7- azaspiro[3.5]nonane-7-carboxylate (50.0 mg, 95.3 umol) in DCM (1 mL) was added HCl/dioxane (4 M, 0.5 mL). The reaction mixture was stirred at 20 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (43.0 mg, 97% yield, HCl salt) as yellow

solid. LC-MS (ESI^+) *m/z* 425.3 $(M+H)^+$.

[00604] Tert-butyl 7-(aminomethyl)-2-azaspiro[3.5]nonane-2-carboxylate (Intermediate AUJ)



AUJ

[00605] Step 1 - 2-Tert-butyl 7-isopropoxycarbonyl 2-azaspiro[3.5]nonane-2,7-dicarboxylate

[00606] To a solution of 2-tert-butoxycarbonyl-2-azaspiro[3.5]nonane-7-carboxylic acid (840 mg, 3.12 mmol, CAS# 1363381-18-3) in THF (10.0 mL) was added Et_3N (1.26 g, 12.5 mmol) and isopropyl carbonochloridate (573 mg, 4.68 mmol). The mixture was stirred at 0 °C for 2 hours. On completion, the mixture was filtered and the filter cake was washed with THF (30 mL). The filtrate was concentrated *in vacuo* to give the title compound (1.10 g, 99 % yield) as yellow oil.

[00607] Step 2 - Tert-butyl 7-(hydroxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate

[00608] To a solution of tert-butyl-isopropoxycarbonyl 2-azaspiro[3.5]nonane-2,7-dicarboxylate (1.10 g, 3.09 mmol) in a mixed solvent of THF (20 mL) and H_2O (1 mL) was added $LiBH_4$ (404 mg, 18.5 mmol). The mixture was stirred at 0 °C for 2 hours. On completion, the reaction mixture was quenched with water (5.0 mL) at 0 °C, and then extracted with (3 X 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (800 mg, 80% yield) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 2H), 3.54 (s, 2H), 3.42 (d, J = 6.4 Hz, 2H), 1.89 (d, J = 13.4 Hz, 2H), 1.76 - 1.67 (m, 3H), 1.45 - 1.39 (m, 12H), 1.01 - 0.89 (m, 2H).

[00609] Step 3 - Tert-butyl 7-(methylsulfonyloxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate

[00610] To a solution of tert-butyl 7-(hydroxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate (800 mg, 3.13 mmol) in DCM (10 mL) was added Et_3N (951 mg, 9.40 mmol). Then MsCl (43.0 mg, 3.76 mmol) was added to the mixture. The mixture was stirred at 0 °C for 2 hours. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was diluted with water (50 mL) and extracted with EA

(3 X 60 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.00 g, 95% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (d, *J* = 6.0 Hz, 2H), 3.60 (d, *J* = 11.6 Hz, 4H), 3.02 (s, 3H), 1.95 (d, *J* = 13.6 Hz, 2H), 1.82 - 1.72 (m, 3H), 1.46 (s, 10H), 1.11 - 1.02 (m, 2H).

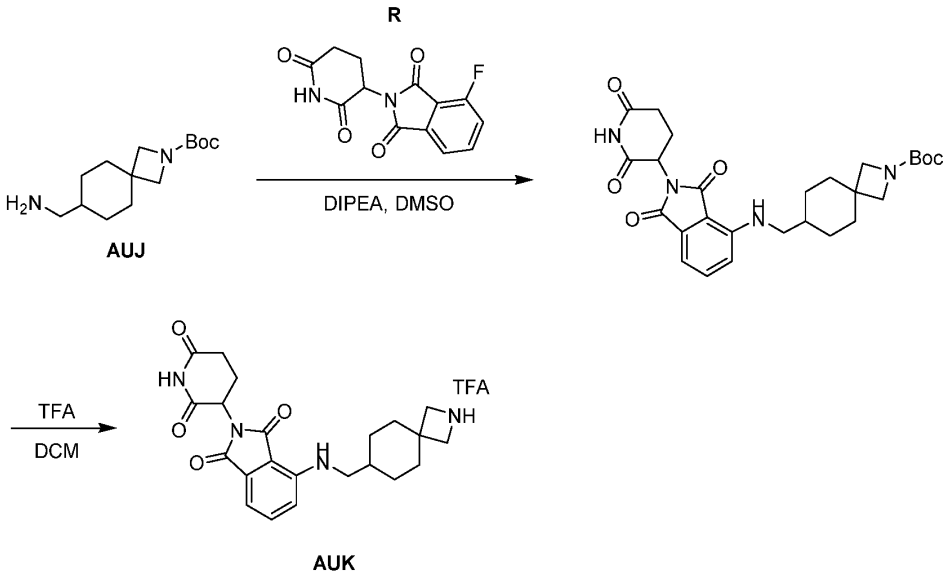
[00611] Step 4 - Tert-butyl 7-[(1,3-dioxoisoindolin-2-yl)methyl]-2-azaspiro[3.5]nonane-2-carboxylate

[00612] To a solution of tert-butyl 7-(methylsulfonyloxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate (1.00 g, 3.00 mmol) in DMF (10 mL) was added (1,3-dioxoisoindolin-2-yl)potassium (833 mg, 4.50 mmol, CAS# 1074-82-4). The mixture was stirred at 80 °C for 2 hours. On completion, the mixture was diluted with water (50 mL) and extracted with EA (3 X 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was triturated with PE/EA (3:1) and the filtered cake was collected and dried *in vacuo* to give the title compound (200 mg, 17 % yield) as white solid. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.81 - 7.76 (m, 2H), 7.70 - 7.62 (m, 2H), 3.53 (s, 2H), 3.48 - 3.44 (m, 3H), 1.82 (d, *J* = 13.2 Hz, 2H), 1.72-1.68 (m, 1H), 1.62 - 1.55 (m, 3H), 1.36 (s, 9H), 1.33 - 1.26 (m, 2H), 1.04 - 0.90 (m, 2H).

[00613] Step 5 - Tert-butyl 7-(aminomethyl)-2-azaspiro[3.5]nonane-2-carboxylate

[00614] To a solution of tert-butyl 7-[(1,3-dioxoisoindolin-2-yl)methyl]-2-azaspiro[3.5]nonane-2-carboxylate (200 mg, 520 umol) in EtOH (5.0 mL) was added $NH_2NH_2.H_2O$ (130 mg, 2.60 mmol). The mixture was stirred at 80 °C for 2 hours. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was washed with DCM (3 X 50 mL) then filtered, and the organic phase was concentrated *in vacuo* to give the title compound (100 mg, 75% yield) as colorless oil.

[00615] 4-(2-Azaspiro[3.5]nonan-7-ylmethylamino)-2-(2,6-dioxo-3-piperidyl) isoindoline-1,3-dione (Intermediate AUK)



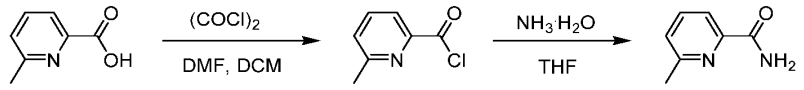
[00616] Step 1 - Tert-butyl 7-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4 -yl]amino]methyl] -2- azaspiro[3.5]nonane-2-carboxylate

[00617] To a solution of tert-butyl 7-(aminomethyl)-2-azaspiro[3.5]nonane-2-carboxylate (100 mg, 393 umol, Intermediate AUJ) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (108 mg, 393 umol, Intermediate R) in DMSO (2 mL) was added DIPEA (50.8 mg, 393 umol). The mixture was stirred at 130 °C for 2 hours. On completion, the mixture was quenched with H_2O (0.2 mL) and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (90.0 mg, 44% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 - 10.96 (m, 1H), 7.57 - 7.53 (m, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 6.8 Hz, 1H), 6.55 (t, J = 6.2 Hz, 1H), 5.05 - 5.00 (m, 1H), 3.52 - 3.41 (m, 4H), 3.13 (t, J = 6.4 Hz, 2H), 2.93 - 2.80 (m, 1H), 2.61 - 2.51 (m, 2H), 2.06 - 1.96 (m, 1H), 1.84 - 1.76 (m, 2H), 1.68 - 1.59 (m, 2H), 1.40 - 1.33 (m, 12H), 1.04 - 0.92 (m, 2H); LC-MS (ESI+) m/z 511.1 $(M+1)^+$.

[00618] Step 2 - 4-(2-Azaspiro[3.5]nonan-7-ylmethylamino)-2-(2,6-dioxo-3-piperidyl) isoindoline-1,3-dione

[00619] To a solution of tert-butyl 7-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl] amino] methyl] -2- azaspiro[3.5]nonane-2-carboxylate (80.0 mg, 156 umol) in DCM (3 mL) was added TFA (1.54 g, 13.5 mmol). The mixture was stirred at 15 °C for 2 hours. On completion, the mixture was concentarted *in vacuo* to give the title compound (64.0 mg, 99.51% yield) as yellow oil. LC-MS (ESI+) m/z 411.3 $(M+1)^+$.

[00620] 6-Methylpyridine-2-carboxamide (Intermediate AXR)



AXR

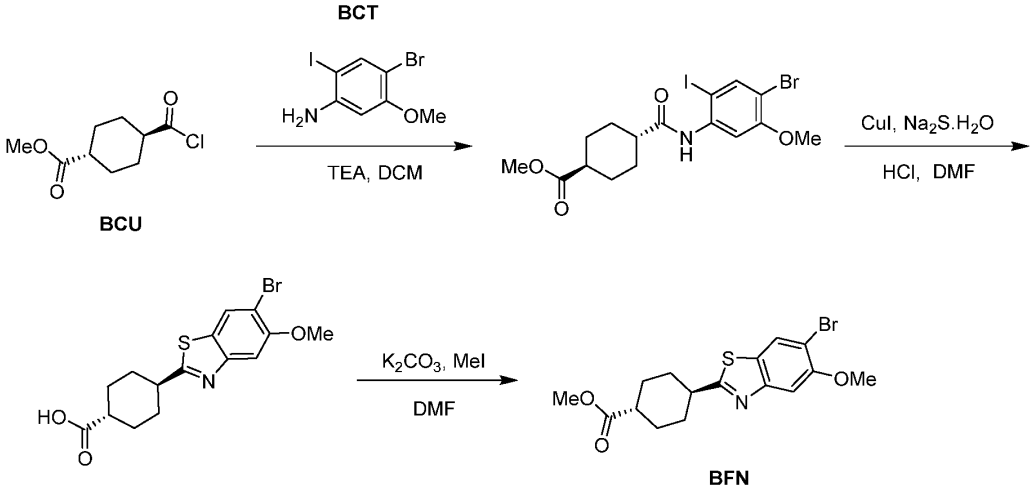
[00621] Step 1 - 6-Methylpyridine-2-carbonyl chloride

[00622] To a solution of 6-methylpyridine-2-carboxylic acid (1.00 g, 7.29 mmol, CAS# 934-60-1) and $(COCl)_2$ (1.11 g, 8.75 mmol) in DCM (10 mL) was added DMF (53.3 mg, 729 umol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. On completion, the reaction was concentrated *in vacuo* to give the title compound (1.10 g, 97% yield) as a white solid.

[00623] Step 2 - 6-Methylpyridine-2-carboxamide

[00624] A solution of 6-methylpyridine-2-carbonyl chloride (1.10 g, 7.07 mmol) in THF (5 mL) was added to $NH_3{\cdot}H_2O$ (9.73 mL, 70.7 mmol , 28% solution) dropwise at 0 °C. The reaction was stirred at 25 °C for 1 hour. On completion, the reaction mixture was diluted with H_2O (20 mL), and extracted with EA (2 X 40 mL). The combined organic phase was dried over Na_2SO_4, and then concentrated *in vacuo* to give the title compound (560 mg, 58% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 - 7.74 (m, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.23 (s, 1H), 2.49 (s, 3H).

[00625] Methyl 4-(6-bromo-5-methoxy-1,3-benzothiazol-2-yl)cyclohexanecarboxylate (Intermediate BFN)



[00626] Step 1 - (1r,4r)-Methyl 4-((4-bromo-2-iodo-5-methoxyphenyl)carbamoyl)cyclohexanecarboxylate

[00627] To a solution of 4-bromo-2-iodo-5-methoxy-aniline (880 mg, 2.68 mmol, Intermediate BCT) and Et3N (814 mg, 8.05 mmol) in the DCM (10 mL) was added methyl 4-

chlorocarbonylcyclohexanecarboxylate (549 mg, 2.68 mmol, Intermediate BCU). The mixture was stirred at 25 °C for 12 hrs. On completion, the reaction mixture was washed with water (50 mL). The organic layer was dried over Na2SO4, filtered and concentrated in vacuo and the residue was triturated with (PE:EA=3:1) to give the title compound (800 mg, 60% yield) as white solid. 1H NMR (400 MHz, CDCl3) δ 8.15 (s, 1H), 7.86 (s, 1H), 7.52 (s, 1H), 3.91 (s, 3H), 3.70 (s, 3H), 2.41 - 2.27 (m, 2H), 2.15 (d, J = 12.6 Hz, 4H), 1.69 - 1.49 (m, 4H).

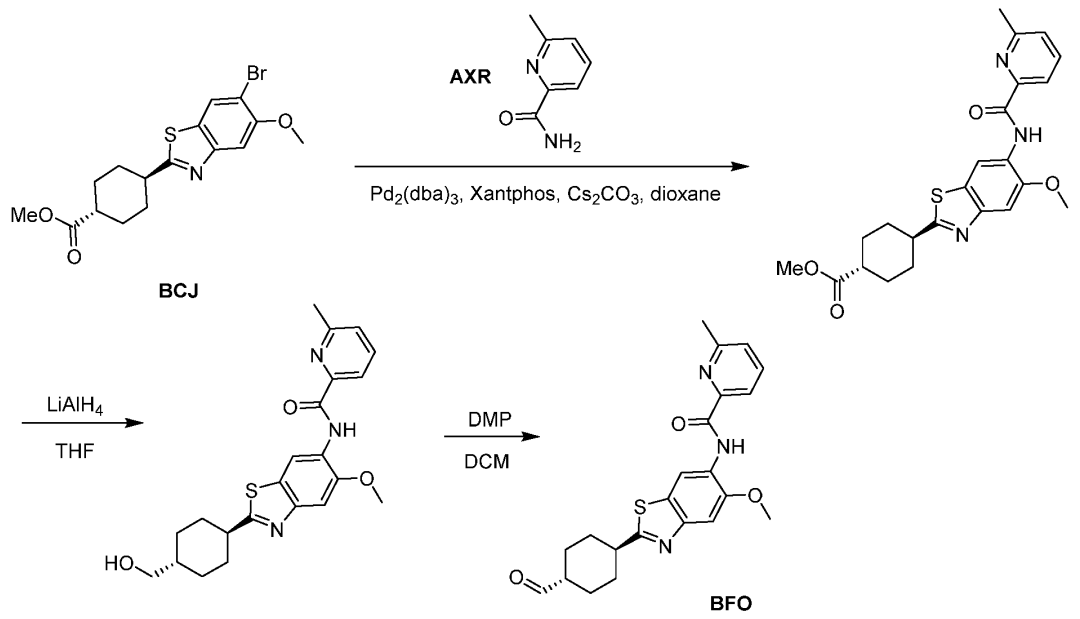
[00628] Step 2 - (1R,4r)-4-(6-Bromo-5-hydroxybenzo[d]thiazol-2-yl)cyclohexanecarboxylic acid

[00629] To a solution of methyl 4-[(4-bromo-2-iodo-5-methoxy-phenyl)carbamoyl]cyclohexanecarboxylate (0.8 g, 1.61 mmol) in the DMF (10 mL) was added $Na_2S·9H_2O$ (774 mg, 3.22 mmol) and CuI (61.4 mg, 322 umol). The mixture was stirred at 80 °C for 12 hrs under N_2. Then the mixture was cooled down to room tempreture and HCl (12 M, 1.34 mL, 36% solution) was added. The mixture was stirred at 25 °C for 5 hrs. On completion, the reaction mixture was diluted with EA (100 mL) and washed with water (3 X 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (570 mg, 99% yield) as yellow solid. LC-MS (ESI^+) m/z 370.2 $(M+H)^+$.

[00630] Step 3 - (1R,4r)-Methyl 4-(6-bromo-5-methoxybenzo[d]thiazol-2-yl)cyclohexanecarboxylate

[00631] To a solution of 4-(6-bromo-5-hydroxy-1,3-benzothiazol-2-yl)cyclohexanecarboxylic acid (567 mg, 1.59 mmol) in the DMF (10 mL) was added K_2CO_3 (440 mg, 3.19 mmol) and MeI (678 mg, 4.78 mmol). The mixture was stirred at 25 °C for 3 hrs. On completion, the reaction mixture was diluted with EA (100 mL) and washed with water (3 X 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* and purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=10/1 to 5/1) to give the title compound (320 mg, 47% yield) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.49 (s, 1H), 3.97 (s, 3H), 3.71 (s, 3H), 3.10 - 3.01 (m, 1H), 2.34 - 2.30 (m, 2H), 2.21 -2.16 (m, 2H), 2.15 -2.10 (m, 1H), 1.75 - 1.61 (m, 4H).

[00632] N-[2-(4-formylcyclohexyl)-5-methoxy-1,3-benzothiazol-6-yl]-6-methyl-pyridine-2-carboxamide (Intermediate BFO)



[00633] Step 1 - Methyl 4-[5-methoxy-6-[(6-methylpyridine-2-carbonyl)amino]-1,3-benzothiazol-2-yl] cyclohexanecarboxylate

[00634] To a solution of methyl 4-(6-bromo-5-methoxy-1,3-benzothiazol-2-yl)cyclohexanecarboxylate (300 mg, 780 umol, Intermediate BFN) and 6-methylpyridine-2-carboxamide (106 mg, 780 umol, Intermediate AXR) in dioxane (8.0 mL) was added Xantphos (90.3 mg, 156 umol), Cs_2CO_3 (508 mg, 1.56 mmol) and $Pd_2(dba)_3$ (71.4 mg, 78.0 umol), and the reaction mixture was stirred at 100 °C for 12 hours. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1 to 4/1) to give the title compound (300 mg, 87% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 9.01 (s, 1H), 7.91 - 8.04 (m, 2H), 7.67 (s, 1H), 7.61 - 7.52 (m, 1H), 4.04 (s, 3H), 3.62 (s, 3H), 3.13 - 3.02 (m, 1H), 2.62 (s, 3H), 2.41 - 2.38 (m, 1H), 2.23 - 2.14 (m, 2H), 2.07 - 1.98 (m, 2H), 1.71 - 1.47 (m, 4H); LC-MS (ESI$^+$) m/z 440.1(M+1)$^+$.

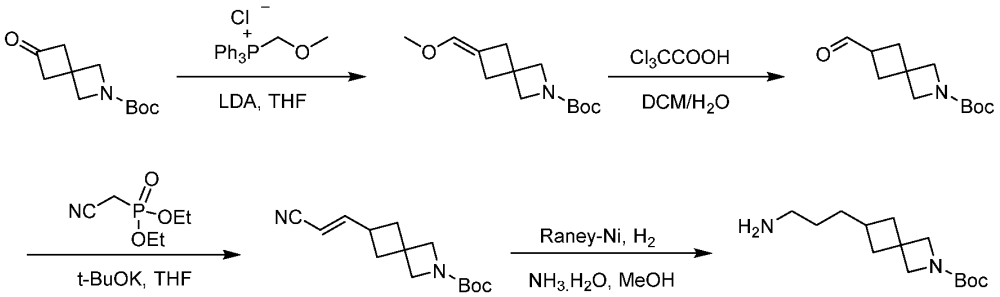
[00635] Step 2 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-methoxy-1,3-benzothiazol-6-yl]-6-methyl-pyridine-2- carboxamide

[00636] To a solution of methyl 4-[5-methoxy-6-[(6-methylpyridine-2-carbonyl)amino]-1,3-benzothiazol-2-yl] cyclohexanecarboxylate (120 mg, 273 umol) in THF (8.0 mL) was added $LiAlH_4$ (20.7 mg, 546 umol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. On completion, the reaction mixture was quenched with H_2O (0.5 mL) and sat. aq NaOH (1.5 mL), and then dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give the title compound (105 mg, 93% yield) as a white solid. LC-MS (ESI$^+$) m/z 412.2(M+1)$^+$.

[00637] Step 3 - N-[2-(4-formylcyclohexyl)-5-methoxy-1,3-benzothiazol-6-yl]-6-methyl-pyridine-2-carboxamide

[00638] To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-6-methoxy-indazol-5-yl]-6-methyl-pyridine-2- carboxamide (100 mg, 253 umol) in DCM (4.0 mL) was added DMP (161 mg, 380 umol), the reaction mixture was stirred at 25 °C for 12 hour. On completion, the reaction mixture was quenched with $Na_2S_2O_3$ (10 mL) and extracted with DCM (2 X 20 mL). The combined organic phase was washed with $NaHCO_3$ and brine (2 X 15 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (95 mg, 95% yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 9.62 (s, 1H), 9.02 (s, 1H), 8.03 - 7.94 (m, 2H), 7.68 (s, 1H), 7.59 - 7.54 (m, 1H), 4.04 (s, 3H), 3.12 - 3.00 (m, 1H), 2.62 (s, 3H), 2.43 - 2.34 (m, 1H), 2.28 - 2.19 (m, 2H), 2.12 - 2.01 (m, 2H), 1.72 - 1.57 (m, 2H), 1.46 - 1.36 (m, 2H); LC-MS (ESI$^+$) m/z 410.2 $(M+1)^+$.

[00639] Tert-butyl 6-(3-aminopropyl)-2-azaspiro[3.3]heptane-2-carboxylate (Intermediate BCL)



BCL

[00640] Step 1 - Tert-butyl 6-(methoxymethylene)-2-azaspiro[3.3]heptane-2-carboxylate

[00641] To a solution of methoxymethyl(triphenyl)phosphonium;chloride (22.7 g, 66.2 mmol, CAS# 4009-98-7) in THF (100 mL) was added dropwise LDA (2 M, 34.7 mL) under N_2 at 0 °C. The reaction mixture was stirred at 25 °C for 2 h. Then a solution of tert-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (7.00 g, 33.1 mmol, CAS# 1181816-12-5) in THF (30 mL) was added dropwise to the mixture. The reaction mixture was stirred at 60 °C for 3 h. On completion, the reaction mixture was concentrated *in vacuo and* diluted with water (30 mL) and extracted with EA (2 X 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to give the title compound (6.96 g, 87% yield) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 - 5.77 (m, 1H), 3.95 - 3.86 (m, 4H), 3.54 (s, 3H), 2.85 (d, J = 2.4 Hz, 2H), 2.78 (d, J = 1.6 Hz, 2H), 1.43 (s, 9H).

[00642] Step 2 - Tert-butyl 6-formyl-2-azaspiro[3.3]heptane-2-carboxylate

[00643] To a mixture of tert-butyl 6-(methoxymethylene)-2-azaspiro[3.3]heptane-2-carboxylate (4.40 g, 18.3 mmol) in DCM (40 mL) and H_2O (20 mL) was added 2,2,2-trichloroacetic acid (12.0 g, 73.5 mmol,

7.42 mL). The reaction mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was diluted with water (30 mL) and extracted with EA (2 X 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to give the title compound (3.00 g, 72% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, J = 1.6 Hz, 1H), 3.93 (s, 2H), 3.82 (s, 2H), 3.14 - 3.02 (m, 1H), 2.47 - 2.30 (m, 4H), 1.42 (s, 9H).

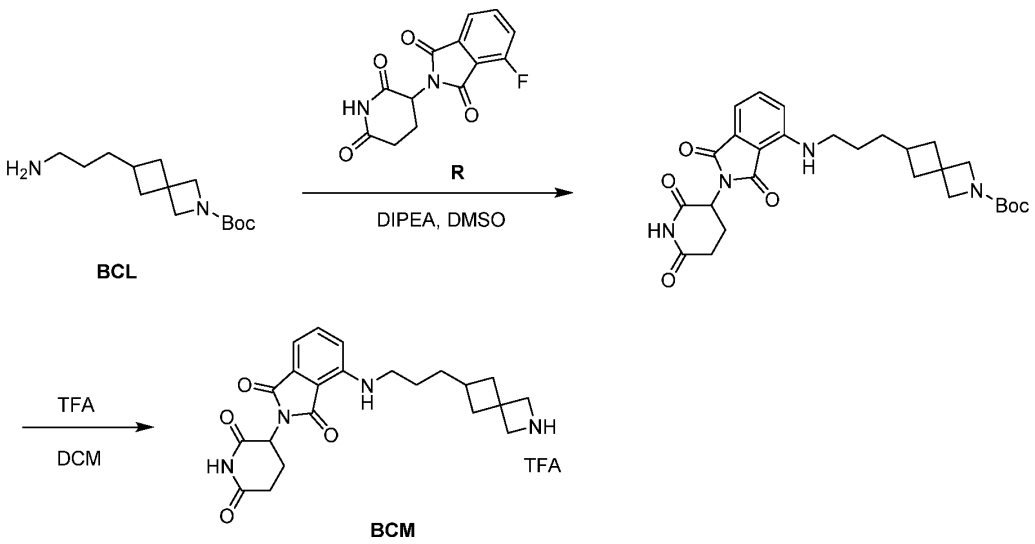
[00644] Step 3 - Tert-butyl 6-[(E)-2-cyanovinyl]-2-azaspiro[3.3]heptane-2-carboxylate

[00645] To a solution of 2-diethoxyphosphorylacetonitrile (4.95 g, 27.9 mmol, CAS# 2537-48-6) in THF (5 mL) was added t-BuOK (3.14 g, 27.9 mmol) at 0 °C dropwise. The mixture was stirred at 25 °C for 0.5 h, then it was cooled to 0 °C and then a solution of tert-butyl 6-formyl-2-azaspiro[3.3]heptane-2 - carboxylate (4.20 g, 18.64 mmol) in THF (5 mL) was added and the reaction was stirred at 25 °C for 16 h. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (2.00 g, 43% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 - 6.68 (m, 1H), 6.47 - 6.40 (m, 2H), 5.28 - 5.23 (m, 1H), 5.22 - 5.19 (m, 2H), 3.99 (s, 3H), 3.96 (s, 2H), 3.83 (s, 3H), 3.82 (s, 2H), 3.40 - 3.29 (m, 2H), 3.01 - 2.93 (m, 1H), 2.56 - 2.48 (m, 4H), 2.45 - 2.38 (m, 2H), 2.12 - 2.12 (m, 1H), 2.17 - 2.10 (m, 3H), 2.10 - 2.06 (m, 2H), 1.43 (s, 14H), 1.42 (s, 9H).

[00646] Step 4 - Tert-butyl 6-(3-aminopropyl)-2-azaspiro[3.3]heptane-2-carboxylate

[00647] To a mixture of tert-butyl 6-[(E)-2-cyanovinyl]-2-azaspiro[3.3]heptane-2-carboxylate (2.00 g, 8.05 mmol) in MeOH (20 mL) and $NH_3{\cdot}H_2O$ (2 mL) was added Raney-Ni (1.38 g, 16.1 mmol). The reaction mixture was stirred at 25 °C for 12 hours under H_2 (50 Psi) atmosphere. On completion, the reaction mixture was filtered and concentrated *in vacuo* to give the title compound (1.90 g, 92% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 2H), 3.78 (s, 2H), 2.72 - 2.48 (m, 2H), 2.31 - 2.19 (m, 2H), 2.14 - 2.02 (m, 1H), 1.78 - 1.67 (m, 2H), 1.42 (s, 9H), 1.39 - 1.28 (m, 4H).

[00648] 4-[3-(2-Azaspiro[3.3]heptan-6-yl)propylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (Intermediate BCM)



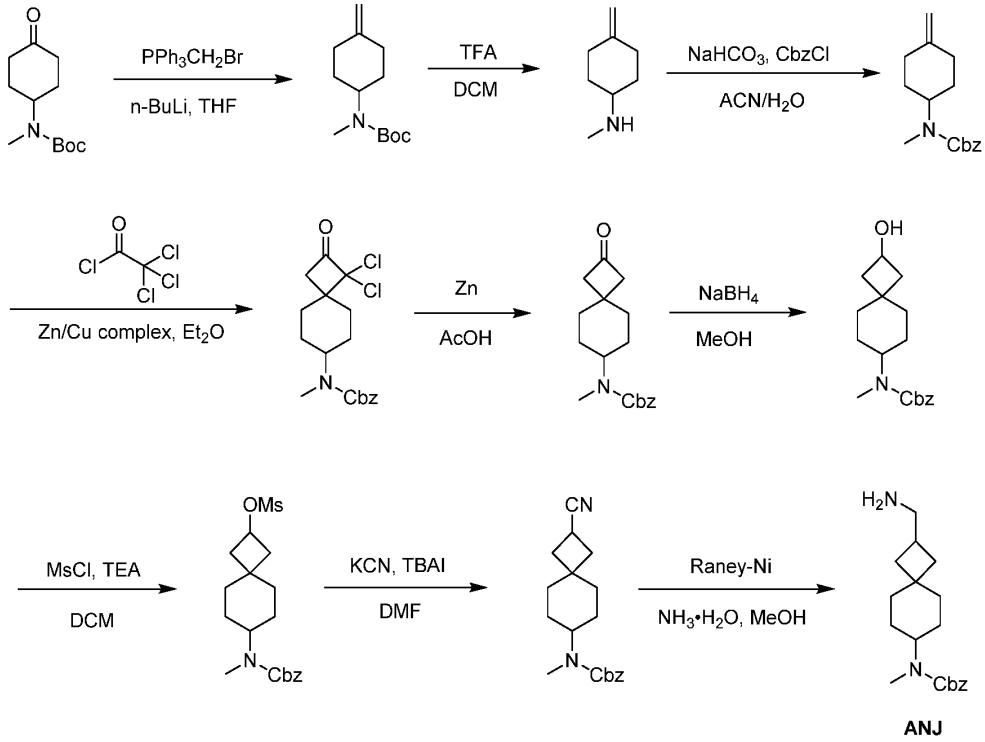
[00649] Step 1 - Tert-butyl 6-[3-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]propyl]-2- azaspiro[3.3]heptane-2-carboxylate

[00650] To a mixture of tert-butyl 6-(3-aminopropyl)-2-azaspiro[3.3]heptane-2-carboxylate (1.90 g, 7.47 mmol, Intermediate BCL) in DMSO (6 mL) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (2.06 g, 7.47 mmol, Intermediate R) was added DIPEA (2.90 g, 22.4 mmol, 3.90 mL). The reaction mixture was stirred at 130 C for 2.5 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (2.30 g, 60% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.60 - 7.53 (m, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 7.0 Hz, 1H), 6.49 (t, J = 5.6 Hz, 1H), 5.09 - 5.01 (m, 1H), 3.82 (s, 2H), 3.70 (s, 2H), 3.28 - 3.21 (m, 2H), 2.95 - 2.82 (m, 1H), 2.63 - 2.51 (m, 2H), 2.26 - 2.16 (m, 2H), 2.11 - 2.00 (m, 2H), 1.76 - 1.68 (m, 2H), 1.52 - 1.42 (m, 2H), 1.42 - 1.36 (m, 2H), 1.35 (s, 9H). LC-MS (ESI$^+$) *m/z* 511.3 (M+H)$^+$.

[00651] Step 2 - 4-[3-(2-Azaspiro[3.3]heptan-6-yl)propylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione

[00652] To a mixture of tert-butyl 6-[3-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]propyl]-2- azaspiro[3.3]heptane-2-carboxylate (80.0 mg, 156 umol) in DCM (2 mL) was added TFA (17.8 mg, 156 umol, 11.6 uL). The reaction mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (82.0 mg, 99% yield, TFA) as red solid. LC-MS (ESI$^+$) *m/z* 411.2 (M+H)$^+$.

[00653] Benzyl N-[2-(aminomethyl)spiro[3.5]nonan-7-yl]-N-methyl-carbamate (Intermediate ANJ)



ANJ

[00654] Step 1 - Tert-butyl N-methyl-N-(4-methylenecyclohexyl)carbamate

[00655] A solution of n-BuLi (2.5 M, 66.0 mL) was added to a mixture of methyltriphenylphosphonium bromide (58.9 g, 165 mmol) in tetrahydrofuran (200 mL) at -10 °C. After stirring for 30 min at -10 °C, the yellow suspension was cooled to -78 °C and a solution of tert-butyl N-methyl-N-(4-oxocyclohexyl)carbamate (25.0 g, 110 mmol, CAS# 400899-84-5) in tetrahydrofuran (100 mL) was added. After stirring for 10 min at -78 °C, the reaction mixture was warmed to 25 °C slowly and stirred for 3 hrs. On completion, the reaction mixture was quenched with saturated ammonium chloride (20 mL), then extracted with ethyl acetate (3 X 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (Petroleum ether/Ethyl acetate= 40/1) to give the title compound (23.7 g, 96% yield) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.66 (s, 2H), 4.33 - 3.94 (m, 1H), 2.72 (s, 3H), 2.47 - 2.32 (m, 2H), 2.24 - 2.10 (m, 2H), 1.84 - 1.75 (m, 2H), 1.54 - 1.49 (m, 2H), 1.48 (m, 9H).

[00656] Step 2 - N-methyl-4-methylene-cyclohexanamine

[00657] To a solution of tert-butyl N-methyl-N-(4-methylenecyclohexyl)carbamate (5.00 g, 22.2 mmol) in DCM (10 mL) was added tertfluoroacetic acid (7.70 g, 67.5 mmol, 5.00 mL). The reaction mixture was stirred at 20 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (5.31 g, 100% yield, TFA salt) as colorless oil. The product was unstable which was used for the

next step without purification. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.77 (s, 2H), 3.27 - 3.06 (m, 1H), 2.76 - 2.73 (m, 3H), 2.50 - 2.42 (m, 2H), 2.22 - 2.05 (m, 4H), 1.58 - 1.50 (m, 2H).

[00658] Step 3 - Benzyl N-methyl-N-(4-methylenecyclohexyl)carbamate

[00659] To a solution of N-methyl-4-methylene-cyclohexanamine (5.31 g, 22.2 mmol, TFA salt) and $NaHCO_3$ (6.53 g, 77.7 mmol, 3.02 mL) in a mixed solvent of ACN (50 mL) and H_2O (50 mL) was added CbzCl (5.68 g, 33.3 mmol, 4.73 mL). The reaction mixture was stirred at 25 °C for 12 hrs. On completion, the reaction mixture was concentrated *in vacuo* to remove ACN, and extracted with ethyl acetate (2 X 100 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 50: 1) to give the title compound (4.00 g, 68% yield) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 - 7.28 (m, 5H), 5.15 (s, 2H), 4.66 (t, J = 1.6 Hz, 2H), 4.33 - 4.01 (m, 1H), 2.79 (s, 3H), 2.37 - 2.34 (m, 2H), 2.18 - 2.15 (m, 2H), 1.87 - 1.73 (m, 2H), 1.57 - 1.48 (m, 2H). LC-MS (ESI^+) *m/z* 260.2 $(M+H)^+$.

[00660] Step 4 - Benzyl N-(3,3-dichloro-2-oxo-spiro[3.5]nonan-7-yl)-N-methyl-carbamate

[00661] To a solution of benzyl N-methyl-N-(4-methylenecyclohexyl)carbamate (3.50 g, 13.5 mmol) in diethyl ether (70 mL) was added Zn/Cu complex (7 g). Then a mixture of 2,2,2-trichloroacetyl chloride (7.36 g, 40.5 mmol, 4.52 mL) in diethyl ether (140 mL) was added dropwise. The reaction mixture was stirred at 30 °C for 16 hrs. On completion, the reaction mixture was poured into saturated $NaHCO_3$ aqueous solution (100 mL) and filtered through a pad of Celite and the filtrate was collected. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to get a residue. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=5/1) to give the title compound (3.80 g, 76% yield) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35 - 7.21 (m, 5H), 5.08 (s, 2H), 4.19 - 4.02 (m, 1H), 2.93 (s, 2H), 2.76 (s, 3H), 2.37 - 2.26 (m, 2H), 1.86 - 1.62 (m, 6H). LC-MS (ESI^+) *m/z* 370.0 $(M+H)^+$.

[00662] Step 5 - Benzyl N-methyl-N-(2-oxospiro[3.5]nonan-7-yl)carbamate

[00663] To a solution of benzyl N-(3,3-dichloro-2-oxo-spiro[3.5]nonan-7-yl)-N-methyl-carbamate (3.30 g, 8.91 mmol) in acetic acid (10 mL) was added Zn (2.33 g, 35.6 mmol) at 15 °C. The reaction mixture was stirred at 80 °C for 3 hrs. On completion, the reaction mixture was filtered and the filtrate was diluted with water (50 mL), then extracted with ethyl acetate (3 X 50 mL). The combined organic layers were washed saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound (2.40 g, 89% yield) as a gum oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.46 - 7.28 (m, 5H), 5.15 (s, 2H), 4.20 - 3.84 (m, 1H), 2.90 - 2.68 (m, 7H), 1.86 - 1.68 (m, 6H), 1.55 - 1.42 (m, 2H); LC-MS (ESI^+) *m/z* 302.2 $(M+H)^+$.

[00664] Step 6 - Benzyl N-(2-hydroxyspiro[3.5]nonan-7-yl)-N-methyl-carbamate

[00665] To a solution of benzyl N-methyl-N-(2-oxospiro[3.5]nonan-7-yl)carbamate (1.00 g, 3.32

mmol) in MeOH (10 mL) was added $NaBH_4$ (151 mg, 3.98 mmol) at 0 °C, and the mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was quenched with water (5 mL). The mixture was concentrated *in vacuo* to remove methanol, then the solution was extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated *in vacuo* to give the title compound (1.00 g, 99% yield) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.44 - 7.28 (m, 5H), 5.14 (s, 2H), 4.28 (q, J = 7.2 Hz, 1H), 4.05 - 3.75 (m, 1H), 2.79 (s, 3H), 2.40 - 2.27 (m, 1H), 2.22 - 2.11 (m, 1H), 1.71 - 1.64 (m, 3H), 1.62 - 1.51 (m, 4H), 1.48 - 1.46 (m, 3H); LC-MS (ESI$^+$) *m/z* 304.1 $(M+H)^+$.

[00666] Step 7 - [7-[Benzyloxycarbonyl(methyl)amino]spiro[3.5]nonan-2-yl] methanesulfonate

[00667] To a solution of benzyl N-(2-hydroxyspiro[3.5]nonan-7-yl)-N-methyl-carbamate (1.00 g, 3.30 mmol) in DCM (20 mL) was added TEA (1.00 g, 9.89 mmol, 1.38 mL) and MsCl (566 mg, 4.94 mmol, 383 uL) at 0 °C . The reaction mixture was stirred at 20 °C for 3 hrs. On completion, the reaction mixture was quenched with water (10 mL). The organic layer was separated and washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound (1.26 g, 100% yield) as yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 - 7.28 (m, 5H), 5.13 (s, 2H), 5.01 - 4.97 (m, 1H), 4.05 - 3.74 (m, 1H), 2.98 (s, 3H), 2.78 (s, 3H), 2.45 (m, 1H), 2.34 - 2.21 (m, 1H), 2.11 - 2.06 (m, 1H), 2.02 - 1.97 (m, 1H), 1.74 - 1.67 (m, 2H), 1.59 - 1.36 (m, 6H). LC-MS (ESI$^+$) *m/z* 382.1 $(M+H)^+$.

[00668] Step 8 - Benzyl N-(2-cyanospiro[3.5]nonan-7-yl)-N-methyl-carbamate

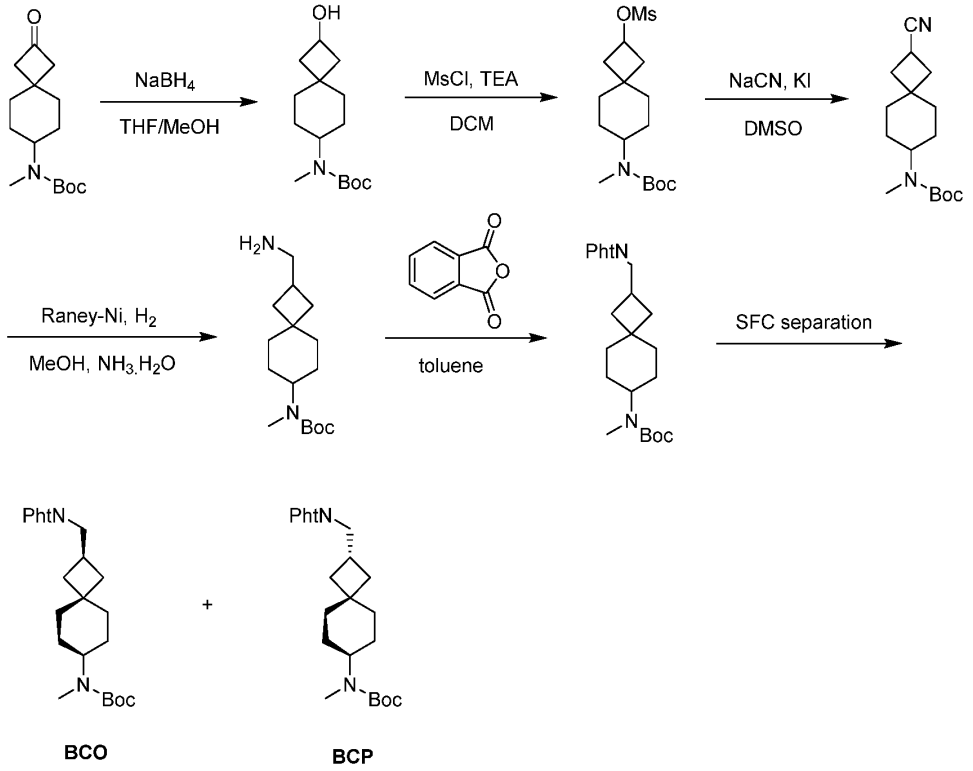
[00669] To a solution of [7-[benzyloxycarbonyl(methyl)amino]spiro[3.5]nonan-2-yl] methanesulfonate (1.26 g, 3.30 mmol) in DMF (10 mL) was added KCN (430 mg, 6.61 mmol, 283 uL) and TBAI (122 mg, 330 umol). The reaction mixture was heated to 120 °C for 16 hrs. On completion, the reaction mixture was diluted with water (10 mL), and extracted with ethyl acetate (3 X 50 mL). The combined organic layers were wash with brine (30 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate= 4/1) to give the title compound (570 mg, 55% yield) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.45 - 7.28 (m, 5H), 5.13 (s, 2H), 4.07 - 3.73 (m, 1H), 3.06 - 2.98 (m, 1H), 2.78 (s, 3H), 2.32 - 2.22 (m, 1H), 2.20 - 2.06 (m, 3H), 1.96 - 1.87 (m, 1H), 1.82 - 1.78 (m, 1H), 1.62 - 1.59(m, 2H), 1.54 - 1.36 (m, 4H). LC-MS (ESI$^+$) *m/z* 313.1 $(M+H)^+$.

[00670] Step 9 - Benzyl N-[2-(aminomethyl)spiro[3.5]nonan-7-yl]-N-methyl-carbamate

[00671] To a solution of benzyl N-(2-cyanospiro[3.5]nonan-7-yl)-N-methyl-carbamate (370 mg, 1.18 mmol) in MeOH (5 mL) was added Raney-Ni (101 mg, 1.18 mmol), $NH_3 \cdot H_2O$ (3.37 g, 31.7 mmol, 3.70 mL, 33% solution) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 25 °C for 4 hours. On completion, the reaction mixture was filtered and concentrated *in vacuo* to give the title compound (300 mg, 84% yield) as colorless oil. ^{1}H NMR

(400MHz, $CDCl_3$) δ 7.47 - 7.29 (m, 5H), 5.15 (s, 2H), 4.89 - 4.50 (m, 2H), 4.04 - 3.78 (m, 1H), 2.79 (s, 3H), 2.69 (d, J = 7.2 Hz, 2H), 2.28 - 2.20 (m, 1H), 2.02 - 1.73 (m, 6H), 1.48 - 1.31 (m, 6H); LC-MS (ESI^+) m/z 317.1 $(M+H)^+$.

[00672] 2-(((((2S,4s,7S)-7-((tert-butoxycarbonyl)(methyl)amino)spiro[3.5]nonan-2-yl)methyl)-l2-azaneyl)carbonyl)benzoic acid (Intermediate BCO) and 2-(((((2R,4r,7R)-7-((tert-butoxycarbonyl)(methyl)amino)spiro[3.5]nonan-2-yl)methyl)-l2-azaneyl)carbonyl)benzoic acid (Intermediate BCP)



[00673] Step 1 - Tert-butyl N-(2-hydroxyspiro[3.5]nonan-7-yl)-N-methyl-carbamate

[00674] To a solution of tert-butyl N-methyl-N-(2-oxospiro[3.5]nonan-7-yl)carbamate (12.0 g, 44.8 mmol, synthesized via Steps 1-5 of Intermediate ANJ) in a mixed solvents of THF (100 mL) and MeOH (30 mL) was added $NaBH_4$ (1.87 g, 49.3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. On completion, the reaction mixture was quenched with sat. aq. NH_4Cl (30 mL), diluted with water (100 mL) and extracted with EA (3 X 200 mL). The combined organic layers were washed with brine (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (11.5 g, 95% yield) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.38 - 4.20 (m, 1H), 4.03 - 3.52 (m, 1H), 2.70 (s, 3H), 2.39 - 2.25 (m, 1H), 2.20 - 2.08 (m, 1H), 1.74 - 1.62 (m, 4H), 1.61 - 1.49 (m, 4H), 1.49 - 1.38 (m, 12H).

[00675] Step 2 - [7-[Tert-butoxycarbonyl(methyl)amino]spiro[3.5]nonan-2-yl] methanesulfonate

[00676] To a solution of tert-butyl N-(2-hydroxyspiro[3.5]nonan-7-yl)-N-methyl-carbamate (15.5 g, 57.5 mmol) and TEA (8.73 g, 86.3 mmol) in DCM (150 mL) was added MsCl (7.91 g, 69.0 mmol) at 0 °C. The reaction mixture was stirred at 0 - 20 °C for 1 hour. On completion, the reaction mixture was diluted with water (100 mL) and extracted with DCM (3 X 100 mL). The combined organic layers were washed with brine (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (19.0 g, 95% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 - 4.96 (m, 1H), 4.00 - 3.59 (m, 1H), 2.98 (s, 3H), 2.70 (s, 3H), 2.53 - 2.40 (m, 1H), 2.33 - 2.21 (m, 1H), 2.17 - 1.93 (m, 2H), 1.75 - 1.66 (m, 2H), 1.61 - 1.47 (m, 4H), 1.46 (s, 9H), 1.44 - 1.34 (m, 2H).

[00677] Step 3 - Tert-butyl N-(2-cyanospiro[3.5]nonan-7-yl)-N-methyl-carbamate

[00678] To a solution of [7-[tert-butoxycarbonyl(methyl)amino]spiro[3.5]nonan-2-yl] methanesulfonate (19.0 g, 54.6 mmol) and KI (13.6 g, 82.0 mmol) in DMSO (200 mL) was added NaCN (4.02 g, 82.0 mmol) at 25 °C. The reaction mixture was stirred at 100 °C for 48 hours. On completion, the reaction mixture was poured into water (400 mL), and extracted with EA (3 X 180 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 20: 1) to give the title compound (9.90 g, 65% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 - 3.51 (m, 1H), 3.04 - 2.97 (m, 1H), 2.69 (s, 3H), 2.31 - 2.21 (m, 1H), 2.17 - 2.07 (m, 3H), 1.94 - 1.84 (m, 1H), 1.82 - 1.72 (m, 1H), 1.60 - 1.50 (m, 2H), 1.50 - 1.46 (m, 1H), 1.45 (s, 9H), 1.44 - 1.34 (m, 3H).

[00679] Step 4 - Tert-butyl N-[2-(aminomethyl)spiro[3.5]nonan-7-yl]-N-methyl-carbamate

[00680] To a solution of tert-butyl N-(2-cyanospiro[3.5]nonan-7-yl)-N-methyl-carbamate (10.5 g, 37.7 mmol) and $NH_3{\cdot}H_2O$ (36.4 g, 259 mmol, 40 mL) in MeOH (100 mL) was added Raney-Ni (969 mg, 11.3 mmol). The reaction mixture was stirred at 25 °C for 16 hours under H_2 (50 psi). On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound (10.1 g, 94% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.88 - 3.56 (m, 1H), 2.62 (s, 3H), 2.55 - 2.51 (m, 2H), 2.26 - 2.04 (m, 1H), 1.95 - 1.74 (m, 2H), 1.72 - 1.63 (m, 1H), 1.62 - 1.40 (m, 4H), 1.38 (s, 9H), 1.37 - 1.22 (m, 5H).

[00681] Step 5 - Tert-butyl N-[2-[(1,3-dioxoisoindolin-2-yl)methyl]spiro[3.5]nonan-7-yl]-N-methyl-carbamate

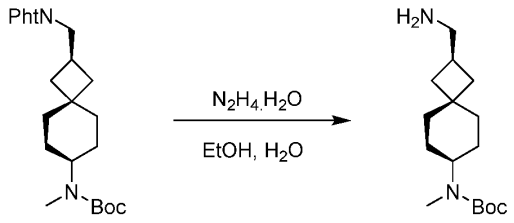
[00682] A mixture of tert-butyl N-[2-(aminomethyl)spiro[3.5]nonan-7-yl]-N-methyl-carbamate (9.80 g, 34.7 mmol) and isobenzofuran-1,3-dione (6.17 g, 41.6 mmol, CAS# 85-44-9) in toluene (100 mL) was stirred at 110 °C for 12 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 20: 1) to give the title compound (11.6 g, 80% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 3.2, 5.6 Hz, 2H), 7.72 (dd, J = 3.2, 5.6 Hz, 2H),

3.98 - 3.53 (m, 3H), 2.73 -2.57 (m, 4H), 2.00 - 1.89 (m, 1H), 1.85 - 1.75 (m, 2H), 1.73 - 1.64 (m, 1H), 1.64 - 1.59 (m, 1H), 1.59 - 1.46 (m, 4H), 1.45 (s, 9H), 1.43 - 1.34 (m, 3H).

[00683] Step 6 - 2-(((((2S,4s,7S)-7-((tert-butoxycarbonyl)(methyl)amino)spiro[3.5]nonan-2-yl)methyl)-l2-azaneyl)carbonyl)benzoic acid (Intermediate BCO) and 2-(((((2R,4r,7R)-7-((tert-butoxycarbonyl)(methyl)amino)spiro[3.5]nonan-2-yl)methyl)-l2-azaneyl)carbonyl)benzoic acid

[00684] Racemic tert-butyl N-[2-[(1,3-dioxoisoindolin-2-yl)methyl]spiro[3.5]nonan-7-yl]-N-methyl-carbamate was separated by SFC ((column: DAICEL CHIRALCEL OJ-H (250mm*30mm, 5um); mobile phase: [0.1%NH_3•H_2O ETOH]) to give the two title compound._The first peak 2-(((((2S,4s,7S)-7-((tert-butoxycarbonyl)(methyl)amino)spiro[3.5]nonan-2-yl)methyl)-l2-azaneyl)carbonyl)benzoic acid (4.80 g, 96% yield, 99% ee) was obtained as colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 3.2, 5.6 Hz, 2H), 7.72 (dd, *J* = 3.2, 5.6 Hz, 2H), 3.97 - 3.62 (m, 3H), 2.75 - 2.57 (m, 4H), 2.00 - 1.90 (m, 1H), 1.86 - 1.74 (m, 2H), 1.72 - 1.64 (m, 1H), 1.63 - 1.54 (m, 2H), 1.54 - 1.46 (m, 3H), 1.45 (s, 9H), 1.43 - 1.33 (m, 3H); LC-MS (ESI$^+$) *m/z* 357.2 $(M+H-56)^+$. The second peak 2-(((((2R,4r,7R)-7-((tert-butoxycarbonyl)(methyl)amino)spiro[3.5]nonan-2-yl)methyl)-l2-azaneyl)carbonyl)benzoic acid (4.90 g, 97% yield, 96.4% ee) was obtained as colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 3.2, 5.6 Hz, 2H), 7.72 (dd, *J* = 3.2, 5.6 Hz, 2H), 3.94 - 3.62 (m, 3H), 2.76 - 2.55 (m, 4H), 2.01 - 1.90 (m, 1H), 1.86 - 1.74 (m, 2H), 1.72 - 1.65 (m, 1H), 1.64 - 1.59 (m, 1H), 1.55 - 1.47 (m, 3H), 1.45 (s, 9H), 1.44 - 1.32 (m, 4H); LC-MS (ESI$^+$) *m/z* 357.2 $(M+H-56)^+$.

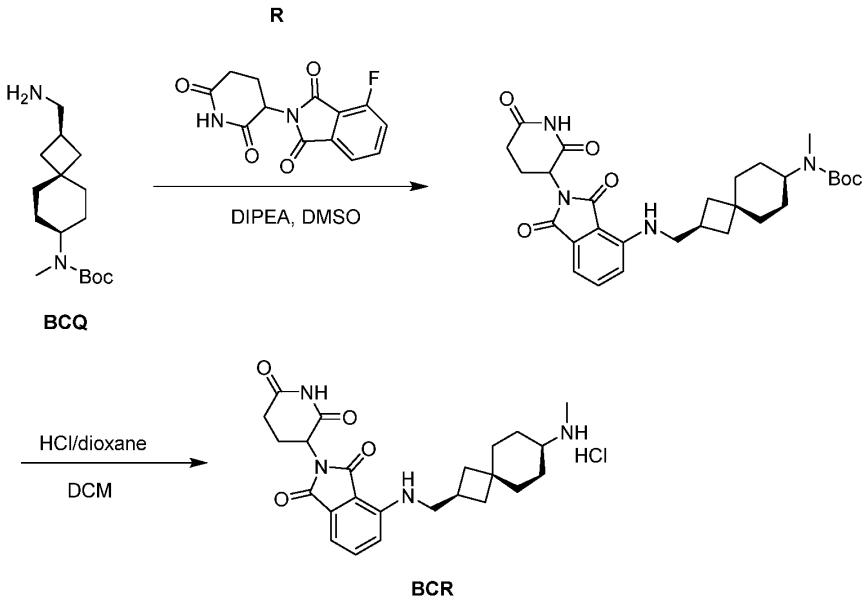
[00685] Tert-butyl N-[2-(aminomethyl)spiro[3.5]nonan-7-yl]-N-methyl-carbamate (Intermediate BCQ)



BCO BCQ

[00686] To a solution of tert-butyl N-[2-[(1,3-dioxoisoindolin-2-yl)methyl]spiro[3.5]nonan-7-yl]-N-methyl- carbamate (450 mg, 1.09 mmol, Intermediate BCO) in EtOH (4 mL) was added N_2H_4·H_2O (222 mg, 4.36 mmol). The reaction mixture was stirred at 80 °C for 2 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was diluted with DCM (100 mL) and filtered *in vacuo*. The filtrate was concentrated *in vacuo* to give the title compound (290 mg, 94% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 2.67 (s, 1H), 2.23 (m, 1H), 1.95 (m, 1H), 1.88 - 1.74 (m, 2H), 1.64 - 1.46 (m, 4H), 1.45 (s, 9H), 1.44 - 1.23 (m, 8H).

[00687] 2-(2,6-Dioxo-3-piperidyl)-4-[[7-(methylamino)spiro[3.5]nonan-2-yl]methylamino]isoindoline-1,3-dione (Intermediate BCR)



[00688] Step 1 - Tert-butyl N-[2-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]methyl]spiro [3.5]nonan-7-yl]-N-methyl-carbamate

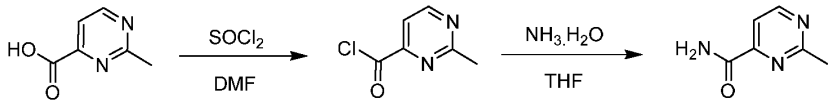
[00689] To a solution of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (283 mg, 1.03 mmol, Intermediate R) and tert-butyl N-[2-(aminomethyl)spiro[3.5]nonan-7-yl]-N-methyl-carbamate (290 mg, 1.03 mmol, Intermediate BCQ) in DMSO (3 mL) was added DIPEA (663 mg, 5.13 mmol). The reaction mixture was stirred at 130 °C for 3 hours. On completion, the reaction mixture was filtered and the filtrate was purified by reversed-phase (0.1% FA) to give the title compound (300 mg, 52% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 - 7.97 (m, 1H), 7.50 (dd, J = 7.2, 8.4 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.19 (t, J = 5.2 Hz, 1H), 4.96 - 4.89 (m, 1H), 4.02 - 3.59 (m, 1H), 3.35 - 3.20 (m, 2H), 2.92 - 2.84 (m, 1H), 2.84 - 2.79 (m, 1H), 2.78 - 2.74 (m, 1H), 2.70 (s, 3H), 2.55 (m, 1H), 2.18 - 2.04 (m, 2H), 1.94 - 1.83 (m, 2H), 1.66 - 1.62 (m, 1H), 1.58 (d, m, 2H), 1.56 - 1.52 (m, 2H), 1.46 (s, 9H), 1.45 - 1.35 (m, 3H).

[00690] Step 2 - 2-(2,6-Dioxo-3-piperidyl)-4-[[7-(methylamino)spiro[3.5]nonan-2-yl]methylamino]isoindoline-1,3-dione

[00691] To a solution of tert-butyl N-[2-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]methyl]spiro [3.5]nonan-7-yl]-Nmethyl-carbamate (290 mg, 538 umol) in DCM (2.5 mL) was added HCl/dioxane (4 M, 2.5 mL). The reaction mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (200 mg, 78% yield, HCl) as

yellow solid. LCMS (ESI^+) m/z 439.2 $(M+H)^+$.

[00692] 2-Methylpyrimidine-4-carboxamide (Intermediate BCR)



BCR

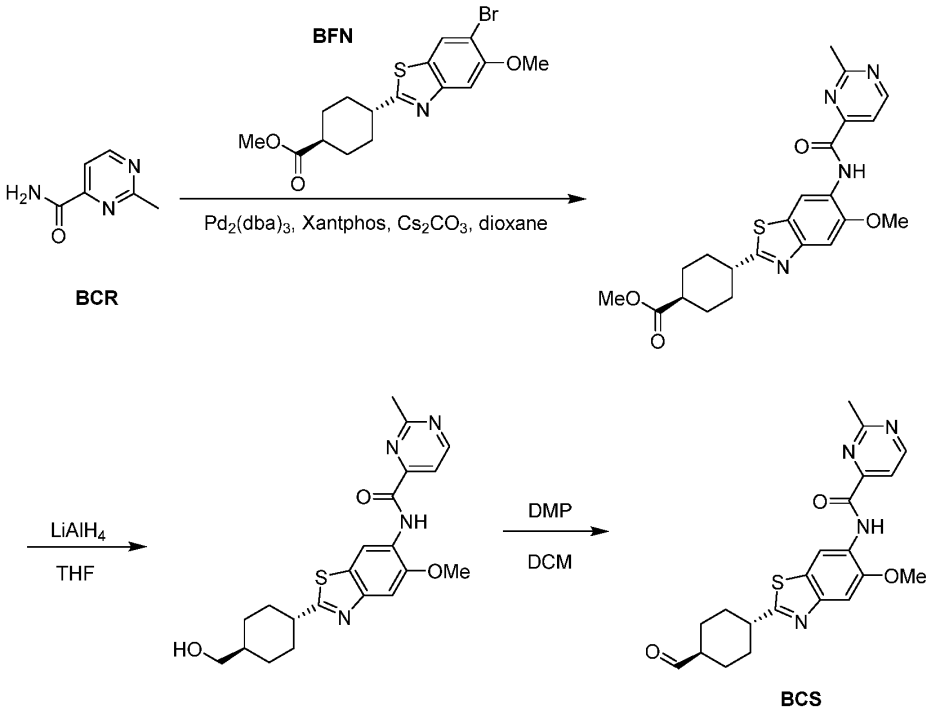
[00693] Step 1 - 2-Methylpyrimidine-4-carbonyl chloride

[00694] A mixture of 2-methylpyrimidine-4-carboxylic acid (2.50 g, 18.1 mmol, CAS# 13627-49-1) and DMF (0.13 g, 0.18 mmol, 0.2 mL) in $SOCl_2$ (30 mL) was stirred at 80 °C for 2 hours. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (2.80 g, 99% yield) as black brown solid.

[00695] Step 2 - 2-Methylpyrimidine-4-carboxamide

[00696] A mixture of 2-methylpyrimidine-4-carbonyl chloride (2.80 g, 17.8 mmol) in THF (20 mL) was added dropwise into $NH_3 \cdot H_2O$ (20 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was diluted with H_2O (20 mL), and then extracted with DCM (3 X 20 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to afford the title compound (1.5 g, 62% yield) as brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.92 (d, J = 5.2 Hz, 1H), 8.21 (s, 1H), 7.90 (s, 1H), 7.79 (d, J = 5.2 Hz, 1H), 2.70 (s, 3H).

[00697] N-[2-(4-formylcyclohexyl)-5-methoxy-1,3-benzothiazol-6-yl]-2-methyl-pyrimidine -4-carboxamide (Intermediate BCS)



[00698] Step 1 - Methyl 4-[5-methoxy-6-[(2-methylpyrimidine-4-carbonyl)amino]-1,3-benzothiazol -2-yl]cyclohexanecarboxylate

[00699] To a mixture of methyl 4-(6-bromo-5-methoxy-1,3-benzothiazol-2-yl)cyclohexanecar boxylate (300 mg, 780 umol, Intermediate BFN) and 2-methylpyrimidine-4-carboxamide (107 mg, 780 umol, Intermediate BCR) in dioxane (8.0 mL) was added $Pd_2(dba)_3$ (71.5 mg, 78.0 umol), Xantphos (90.3 mg, 156 umol) and Cs_2CO_3 (508 mg, 1.56 mmol). The mixture was stirred at 100 °C under N_2 atmosphere for 16 hours. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to afford the title compound (250 mg, 72% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 9.05 (d, J = 5.2 Hz, 1H), 8.99 (s, 1H), 7.98 (d, J = 5.2 Hz, 1H), 7.71 (s, 1H), 4.05 (s, 3H), 3.62 (s, 3H), 3.14 - 3.06 (m, 1H), 2.79 (s, 3H), 2.44 - 2.40 (m, 1H), 2.23 - 2.16 (m, 2H), 2.07 - 2.01 (m, 2H), 1.64 - 1.52 (m, 4H). LC-MS (ESI$^+$) *m/z* 441.2 $(M+H)^+$.

[00700] Step 2 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-methoxy-1,3-benzothiazol-6-yl]-2-methyl-pyrimidine-4-carboxamide

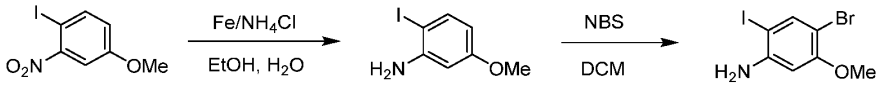
[00701] To a mixture of methyl 4-[5-methoxy-6-[(2-methylpyrimidine-4-carbonyl)amino]-1,3- benzo thiazol-2-yl]cyclohexanecarboxylate (200 mg, 454 umol) in THF (8.0 mL) was added $LiAlH_4$ (34.5 mg, 908 umol) at -20 °C. The mixture was warmed to 0 °C and stirred at this temperature for 2 hours. On completion, the reaction mixture was quenched with saturated aq. NH_4Cl (10 mL) at 0 °C, diluted with H_2O

(30 mL) and extracted with DCM (3 X 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (130 mg, 69% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 9.05 (d, J = 5.2 Hz, 1H), 8.97 (s, 1H), 7.97 (d, J = 5.2 Hz, 1H), 7.70 (s, 1H), 4.49 - 4.39 (m, 1H), 4.04 (s, 3H), 3.29 - 3.25 (m, 2H), 3.07 - 2.97 (m, 1H), 2.79 (s, 3H), 2.22 - 2.12 (m, 2H), 1.92 - 1.82 (m, 2H), 1.62 - 1.50 (m, 2H), 1.49 - 1.38 (m, 1H), 1.16 - 1.03 (m, 2H); LC-MS (ESI+) *m/z* 413.1 $(M+H)^+$.

[00702] Step 3 - N-[2-(4-formylcyclohexyl)-5-methoxy-1,3-benzothiazol-6-yl]-2-methyl-pyrimidine - 4-carboxamide

[00703] To a mixture of N-[2-[4-(hydroxymethyl) cyclohexyl]-5-methoxy-1,3-benzothiazol-6-yl]-2-methyl-pyrimidine-4-carboxamide (100 mg, 242 umol) in DCM (10.0 mL) was added DMP (133 mg, 315 umol) at 25 °C. The mixture was stirred at 25 °C for 3 hours. On completion, the reaction mixture was quenched with saturated aq. Na_2SO_3 (10 mL) and aq. NH_4Cl (10 mL) at 25 °C, and then extracted with DCM (3 X 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (90.0 mg, 90% yield) as yellow solid. LC-MS (ESI+) *m/z* 411.2 $(M+H)^+$.

[00704] 4-Bromo-2-iodo-5-methoxyaniline (Intermediate BCT)



BCT

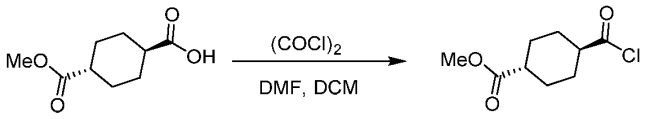
[00705] Step 1 - 2-Iodo-5-methoxyaniline

[00706] To a solution of 1-iodo-4-methoxy-2-nitro-benzene (12.5 g, 44.8 mmol, CAS# 58755-70-7) in the EtOH (200 mL) and H_2O (40 mL) was added NH_4Cl (24.0 g, 448 mmol) and Fe (15.0 g, 269 mmol). The mixture was refluxed at 80 °C for 3 hrs. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (10.5 g, 94% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.6 Hz, 1H), 6.34 (d, J = 2.8 Hz, 1H), 6.14 (dd, J = 2.8, 8.4 Hz, 1H), 4.08 (s, 2H), 3.75 (s, 3H).

[00707] Step 2 - 4-Bromo-2-iodo-5-methoxyaniline

[00708] To a solution of 2-iodo-5-methoxy-aniline (5.00 g, 20.1 mmol) in the DCM (100 mL) was added NBS (3.57 g, 20.1 mmol). The mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, PE: EA = 10:1 to 5:1) to give the title compound (6.30 g, 96% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.33 (s, 1H), 4.13 (s, 2H), 3.83 (s, 3H).

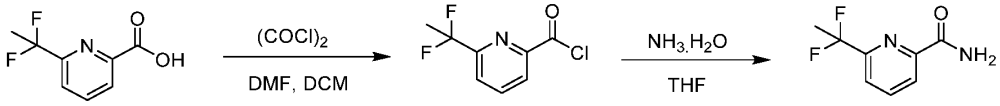
[00709] (1R,4r)-Methyl 4-(chlorocarbonyl)cyclohexanecarboxylate (Intermediate BCU)



BCU

[00710] To a solution of 4-methoxycarbonylcyclohexanecarboxylic acid (500 mg, 2.69 mmol) in the DCM (10 mL) was added DMF (19.6 mg, 268 umol, 20.6 uL) and $(COCl)_2$ (511 mg, 4.03 mmol). The mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (549 mg, 99% yield) as yellow oil.

[00711] 6-(1,1-Difluoroethyl)picolinamide (Intermediate BAD)



BAD

[00712] Step 1 - 6-(1,1-Difluoroethyl)picolinic acid

[00713] To a solution of methyl 6-(1, 1-difluoroethyl)pyridine-2-carboxylate (27.0 g, 134 mmol, CAS# 1211529-86-0) in methanol (40 mL) and THF (80 mL) was added a solution of $LiOH.H_2O$ (11.2 g, 268 mmol) in H_2O (20 mL). The mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was acidified with 4 N aq.HCl till pH = 3. The precipitated solid was filtered, collected and dried to give the title compound (22.0 g, 86% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 14.26 - 12.46 (m, 1H), 8.22 - 8.10 (m, 2H), 7.96 - 7.86 (m, 1H), 2.03 (t, J = 19.2 Hz, 3H).

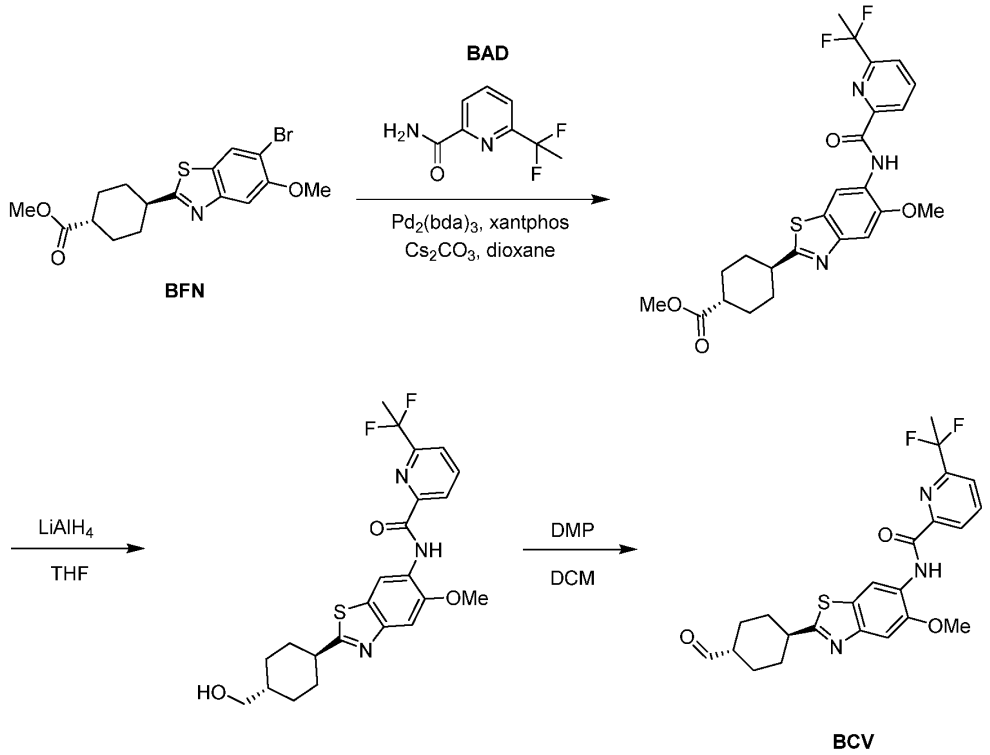
[00714] Step 2- 6-(1,1-Difluoroethyl)picolinoyl chloride

[00715] To a solution of 6-(1,1-difluoroethyl)pyridine-2-carboxylic acid (22.0 g, 117 mmol) in DCM (220 mL) and DMF (859 mg, 11.76 mmol) was added $(COCl)_2$ (29.8 g, 235.11 mmol) dropwise at 0 °C. The mixture was stirred at 25 °C for 0.5 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (24.0 g, 100% yield) as a yellow solid.

[00716] Step 3 - 6-(1,1-Difluoroethyl)picolinamide

[00717] A solution of 6-(1,1-difluoroethyl)pyridine-2-carbonyl chloride (24.0 g, 116 mmol) in THF (100 mL) was added to $NH_3{\cdot}H_2O$ (146 g, 1.17 mol, 28% solution) dropwise at 0 °C. The mixture was stirred at 25 °C for 0.5 hour. On completion, the residue was diluted with H_2O (100 mL) and extracted with EA (3 X 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (18.0 g, 81% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.26 - 8.10 (m, 3H), 7.90 (s, 1H), 7.78 (s, 1H), 2.12 (t, J = 19.2 Hz, 3H).

[00718] 6-(1,1-Difluoroethyl)-N-(2-((1r,4r)-4-formylcyclohexyl)-5-methoxybenzo[d]thiazol-6-yl) picolinamide (Intermediate BCV)



[00719] Step 1 - (1R,4r)-Methyl 4-(6-(6-(1,1-difluoroethyl)picolinamido)-5-methoxybenzo[d]thiazol-2-yl) cyclohexanecarboxylate

[00720] To a solution of methyl 4-(6-bromo-5-methoxy-1,3-benzothiazol-2-yl)cyclohexanecarboxylate (380 mg, 988 umol, Intermediate BFN) and 6-(1,1-difluoroethyl)pyridine-2-carboxamide (193 mg, 1.04 mmol, Intermediate BAD) in dioxane (4 mL) was added $Pd_2(dba)_3$ (90.5 mg, 98.8 umol), Xantphos (114 mg, 197 umol) and Cs_2CO_3 (644 mg, 1.98 mmol). The mixture was stirred at 100 °C for 6 hrs under N_2. On completion, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 5/1) to give the title compound (415 mg, 86% yield) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 9.13 (s, 1H), 8.38 (d, J = 7.2 Hz, 1H), 8.07 (t, J = 7.6 Hz, 1H), 7.88 (dd, J = 0.8, 7.6 Hz, 1H), 7.53 (s, 1H), 4.04 (s, 3H), 3.71 (s, 3H), 3.12 -3.02 (m, 1H), 2.47 - 2.39 (m, 1H), 2.37 - 2.30 (m, 2H), 2.23 - 2.12 (m, 2H), 1.77 - 1.64 (m, 4H).

[00721] Step 2 - 6-(1,1-Difluoroethyl)-N-(2-((1r,4r)-4-(hydroxymethyl)cyclohexyl)-5-methoxybenzo[d] thiazol-6-yl)picolinamide

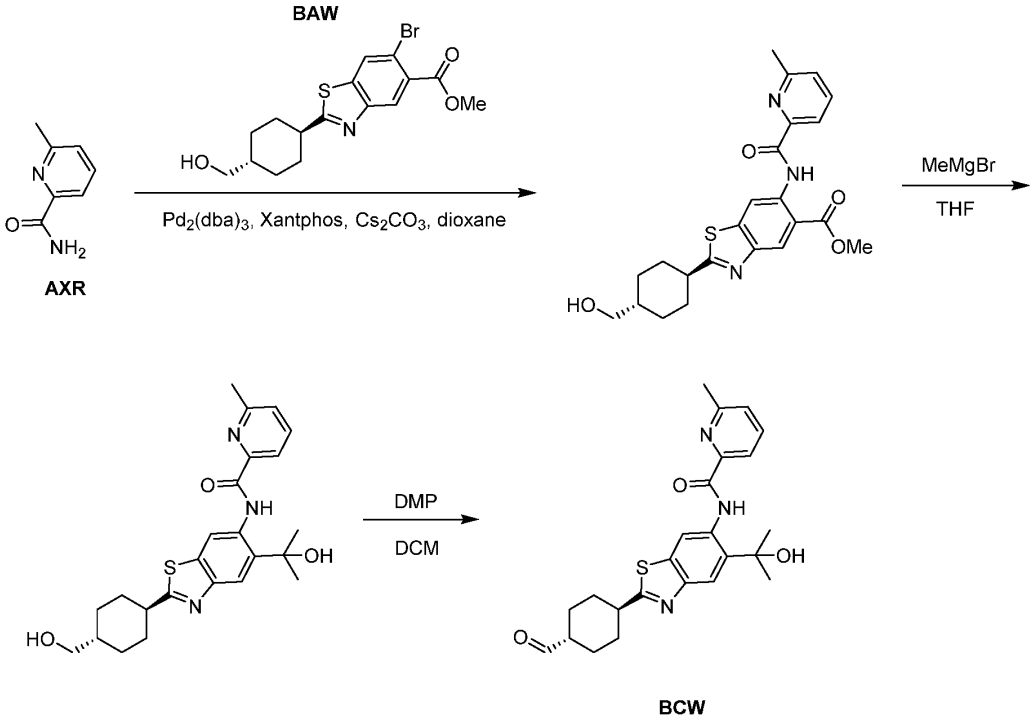
[00722] To a solution of methyl 4-[6-[[6-(1,1-difluoroethyl)pyridine-2-carbonyl]amino]-5-methoxy-

1,3- benzothiazol-2-yl]cyclohexanecarboxylate (100 mg, 204 umol) in the THF (2 mL) was added $LiAlH_4$ (15.5 mg, 408 umol) at -40 °C and the mixture was stirred at -40 °C for 1 hr. On completion, the reaction mixture was quenched by water (0.1 mL) and NaOH (15% aq, 0.1 mL) at 0 °C. Then the mixture was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (94 mg, 99% yield) as yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 9.13 (s, 1H), 8.38 (d, J = 7.6 Hz, 1H), 8.07 (t, J = 7.6 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.54 (s, 1H), 4.05 (s, 3H), 3.55 (d, J = 6.4 Hz, 2H), 3.10- 3.00 (m, 1H), 2.36 - 2.27 (m, 2H), 2.18 (t, J = 18.4 Hz, 3H), 2.04 - 1.96 (m, 2H), 1.76 - 1.64 (m, 3H), 1.26 - 1.14 (m, 2H).

[00723] Step 3 - 6-(1,1-Difluoroethyl)-N-(2-((1r,4r)-4-formylcyclohexyl)-5-methoxybenzo[d]thiazol-6-yl) picolinamide

[00724] To a solution of 6-(1,1-difluoroethyl)-N-[2-[4-(hydroxymethyl)cyclohexyl]-5-methoxy-1,3-benzothiazol-6-yl]pyridine-2-carboxamide (94.0 mg, 203 umol) in the DCM (1 mL) was added DMP (95.0 mg, 224 umol). The mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was quenched by the addition of $Na_2S_2O_3$ (aq. 3 mL) and $NaHCO_3$ (aq. 3mL). Then the mixture was extracted with DCM (2 X 20mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (90 mg, 96% yield) as yellow solid. LC-MS (ESI^+) m/z 460.2 $(M+H)^+$.

[00725] N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-methyl-pyridine-2-carboxamide (Intermediate BCW)



[00726] Step 1 - Methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-[(6-methylpyridine-2-carbonyl)amino]-1,3- benzothiazole-5-carboxylate

[00727] To a solution of methyl 6-bromo-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazole-5-carboxylate (500 mg, 1.30 mmol, Intermediate BAW) and 6-methylpyridine-2-carboxamide (194 mg, 1.43 mmol, Intermediate AXR) in dioxane (3 mL) was added Xantphos (150 mg, 260 umol), Cs_2CO_3 (1.70 g, 5.20 mmol) and $Pd_2(dba)_3$ (119 mg, 130 umol) at 25 °C. The reaction mixture was stirred at 80 °C for 12 hrs under N_2. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 3/1) to give the title compound (140 mg, 24% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 9.47 (s, 1H), 8.53 (s, 1H), 8.05 - 7.93 (m, 2H), 7.57 (dd, J = 0.8, 7.2 Hz, 1H), 4.45 (t, J = 5.6 Hz, 1H), 4.00 (s, 3H), 3.30 - 3.25 (m, 2H), 3.12 - 3.03 (m, 1H), 2.65 (s, 3H), 2.23 - 2.13 (m, 2H), 1.92 - 1.83 (m, 2H), 1.63 - 1.52 (m, 2H), 1.48 - 1.40 (m, 1H), 1.15 - 1.01 (m, 2H); LC-MS (ESI+) m/z 440.2 $(M+H)^+$.

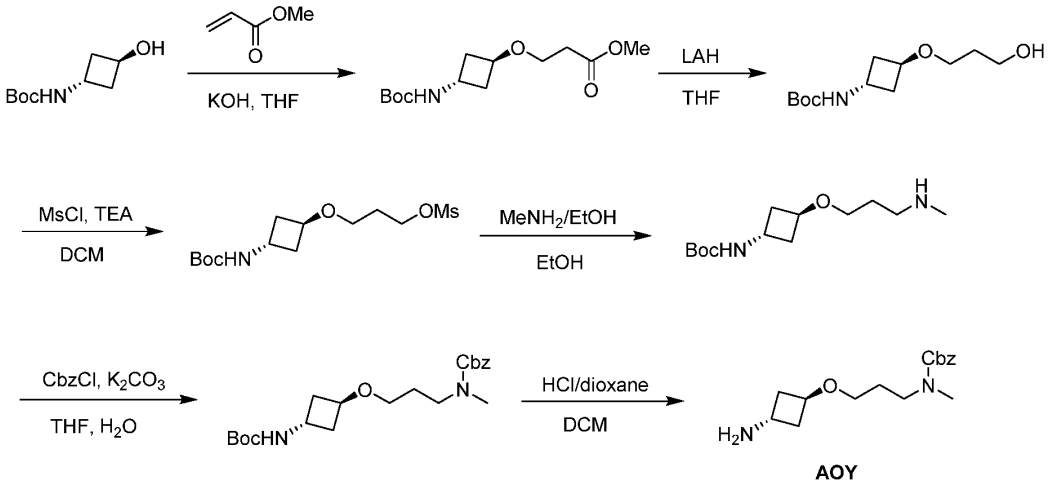
[00728] Step 2 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl] -6-methyl-pyridine-2-carboxamide

[00729] To a solution of methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-[(6-methylpyridine-2-carbonyl)amino] -1,3-benzothiazole-5-carboxylate (100 mg, 227 umol) in THF (1.5 mL) was added MeMgBr (3 M, 758 uL) at 0 °C. The mixture was stirred at 0-25 °C for 2 hrs. On completion, the reaction mixture was quenched by addition 5 mL sat.aq NH_4Cl at 0 °C and was diluted with 60 mL H_2O and extracted with EA 30 mL (3 X 10 mL). The combined organic layers were washed by brine (20 mL), dried over by Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 2/1) to give the title compound (96.0 mg, 95% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 9.07 (s, 1H), 8.00 - 7.92 (m, 2H), 7.88 (s, 1H), 7.55 - 7.50 (m, 1H), 6.04 (s, 1H), 4.45 (t, J = 5.6 Hz, 1H), 3.27 (t, J = 5.6 Hz, 2H), 3.08 - 2.98 (m, 1H), 2.61 (s, 3H), 2.22 - 2.13 (m, 2H), 1.92 - 1.82 (m, 2H), 1.64 (s, 6H), 1.61 - 1.51 (m, 2H), 1.49 - 1.38 (m, 1H), 1.15 - 1.04 (m, 2H).

[00730] Step 3 - N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-methyl- pyridine-2-carboxamide

[00731] To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol -6-yl]-6-methyl-pyridine-2-carboxamide (86.0 mg, 195 umol) in DCM (1.5 mL) was added DMP (107 mg, 254 umol) at 25°C.The reaction mixture was stirred at 25 °C for 2 hrs. On completion, the reaction mixture was quenched with 3 mL sat.aq. $Na_2S_2O_3$ and 3 mL $NaHCO_3$, and then diluted with 3 mL H_2O. The mixture was extracted with DCM (3 X 8 mL). The combined organic layers were washed with brine 10 mL (2 X 5 mL), dried over by Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (85.0 mg, 99% yield) as a brown solid. LC-MS (ESI+) m/z 420.2 $(M-17)^+$.

[00732] Benzyl N-[3-(3-aminocyclobutoxy)propyl]-N-methyl-carbamate (Intermediate AOY)



AOY

[00733] Step 1 - Methyl 3-[3-(tert-butoxycarbonylamino)cyclobutoxy]propanoate

[00734] To a solution of tert-butyl N-(3-hydroxycyclobutyl)carbamate (2.50 g, 13.3 mmol, CAS# 389890-42-0) and methyl prop-2-enoate (2.30 g, 26.7 mmol, CAS# 96-33-3) in THF (25 mL) was added KOH (74.9 mg, 1.34 mmol). The reaction mixture was stirred at 20 °C for 16 hrs. On completion, the reaction mixture was diluted with water (80 mL) and extracted with EA (3 X 80 mL). The combined organic layers were washed with brine (2 X 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 8: 1) to give the title compound (1.80 g, 49% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 - 4.59 (m, 1H), 4.26 - 4.03 (m, 2H), 3.70 (s, 3H), 3.59 (t, J = 6.4 Hz, 2H), 2.57 (t, J = 6.4 Hz, 2H), 2.42 - 2.30 (m, 2H), 2.19 - 2.06 (m, 2H), 1.44 (s, 9H).

[00735] Step 2 - Tert-butyl N-[3-(3-hydroxypropoxy)cyclobutyl]carbamate

[00736] To a solution of methyl 3-[3-(tert-butoxycarbonylamino)cyclobutoxy]propanoate (1.80 g, 6.59 mmol) in THF (20 mL) was added LAH (274 mg, 7.24 mmol). The reaction mixture was stirred at 0 °C for 1 hr. On completion, the reaction mixture was quenched by water (0.25mL), added 15% NaOH (0.3 mL), water (0.8 mL), diluted with EA (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.50 g, 92.% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (s, 1H), 4.54 - 4.41 (m, 1H), 4.27 - 4.14 (m, 1H), 4.12 - 4.04 (m, 1H), 3.81 - 3.74 (m, 2H), 3.50 (t, J = 6.0 Hz, 2H), 2.37 - 2.30 (m, 2H), 2.24 -2.14 (m, 2H), 1.86 - 1.80 (m, 2H), 1.44 (s, 9H).

[00737] Step 3 - 3-[3-(Tert-butoxycarbonylamino)cyclobutoxy]propyl methanesulfonate

[00738] To a solution of tert-butyl N-[3-(3-hydroxypropoxy)cyclobutyl]carbamate (1.50 g, 6.11 mmol) and TEA (928 mg, 9.17 mmol) in DCM (20 mL) was added MsCl (840 mg, 7.34 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr. On completion, the reaction mixture was diluted with water (20 mL)

and extracted with DCM (3 X 40 mL). The combined organic layers were washed with brine (2 X 30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.90 g, crude) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 - 5.11 (m, 1H), 4.79 - 4.66 (m, 1H), 4.34 (t, *J* = 6.0 Hz, 2H), 4.09 - 4.04 (m, 1H), 3.42 (t, *J* = 6.0 Hz, 2H), 3.02 (s, 3H), 2.51 - 2.26 (m, 4H), 2.00 (q, *J* = 6.0 Hz, 2H), 1.44 (s, 9H).

[00739] Step 4 - Tert-butyl N-[3-[3-(methylamino)propoxy]cyclobutyl]carbamate

[00740] A mixture of 3-[3-(tert-butoxycarbonylamino)cyclobutoxy]propyl methanesulfonate (1.90 g, 5.87 mmol) and $MeNH_2$/EtOH (5.87 mmol, 10 mL, 30% solution) was stirred at 70 °C for 12 hrs in a sealed tube (15 psi). On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (1.80 g, crude) as yellow oil and used for next step directly. LC-MS (ESI^+) *m/z* 259.0 $(M+H)^+$.

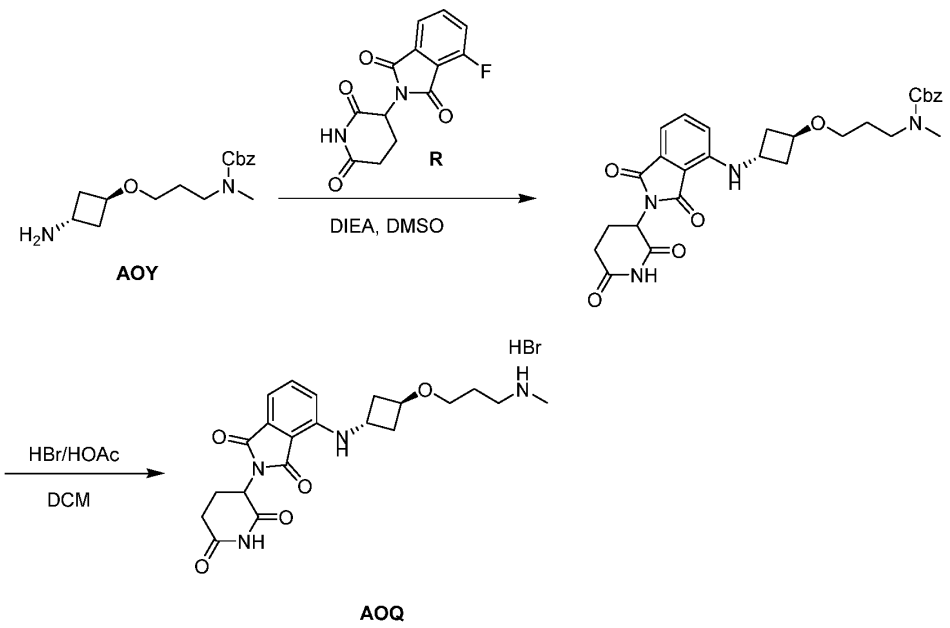
[00741] Step 5 - Benzyl N-[3-[3-(tert-butoxycarbonylamino)cyclobutoxy]propyl]-N-methyl-carbamate

[00742] To a solution of tert-butyl N-[3-[3-(methylamino)propoxy]cyclobutyl]carbamate (1.80 g, 6.97 mmol) and K_2CO_3 (1.93 g, 13.9 mmol) in a mixed solvents of THF (15 mL) and water (5 mL) was added CbzCl (1.78 g, 10.4 mmol). The reaction mixture was stirred at 20 °C for 2 hrs. On completion, the reaction mixture was diluted with water (30 mL) and extracted with EA (3 X 50 mL). The combined organic layers were washed with brine (2 X 30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 5:1) to give the title compound (1.30 g, 41% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.29 (m, 5H), 5.13 (s, 2H), 4.79 - 4.58(m, 1H), 4.32 - 4.14 (m, 1H), 4.07 - 3.92 (m, 1H), 3.42 - 3.21 (m, 4H), 2.94 (s, 3H), 2.39 - 2.23 (m, 2H), 2.14 - 2.05 (m, 2H), 1.87 - 1.72 (m, 2H), 1.45 (s, 9H).

[00743] Step 6 - Benzyl N-[3-(3-aminocyclobutoxy)propyl]-N-methyl-carbamate

[00744] To a solution of benzyl N-[3-[3-(tert-butoxycarbonylamino)cyclobutoxy]propyl]-N-methyl-carbamate (1.60 g, 4.08 mmol) in DCM (20 mL) was added HCl/dioxane (4 M, 15 mL). The reaction mixture was stirred at 20 °C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (1.30 g, 96% yield, HCl salt) as yellow semisolid. LC-MS (ESI^+) *m/z* 293.2 $(M+H)^+$.

[00745] 2-(2,6-dioxo-3-piperidyl)-4-[[3-[3-(methylamino)propoxy]cyclobutyl]amino] isoindoline-1,3-dione (Intermediate AOQ)



[00746] Step 1 - Benzyl N-[3-[3-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]cyclobutoxy] propyl]-N-methyl-carbamate

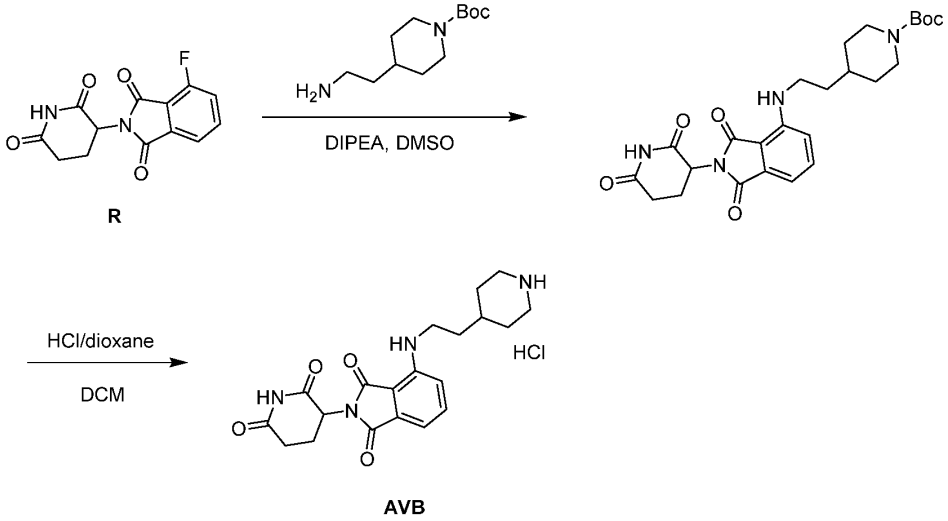
[00747] To a solution of benzyl N-[3-(3-aminocyclobutoxy)propyl]-N-methyl-carbamate (1.30 g, 3.95 mmol, HCl salt, Intermediate AOY) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (928 mg, 3.36 mmol, Intermediate R) in DMSO (15 mL) was added DIPEA (2.55 g, 19.7 mmol). The reaction mixture was stirred at 130 °C for 3 hrs. On completion, the reaction mixture was diluted with water (50 mL) and extracted with EA (3 X 70 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase (0.1% FA) to give the title compound (810 mg, 37% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.54 - 7.47 (m, 1H), 7.42 - 7.28 (m, 5H), 7.14 (d, J = 7.2 Hz, 1H), 6.80 - 6.64 (m, 1H), 6.36 - 6.22 (m, 1H), 5.14 (s, 2H), 4.99 - 4.87 (m, 1H), 4.24 - 4.05 (m, 2H), 3.47 - 3.28 (m, 4H), 2.95 (s, 3H), 2.93 - 2.84 (m, 1H), 2.84 - 2.70 (m, 2H), 2.57 - 2.35 (m, 2H), 2.28 - 2.09 (m, 3H), 1.90-1.74 (m, 2H).

[00748] Step 2 - 2-(2,6-Dioxo-3-piperidyl)-4-[[3-[3-(methylamino)propoxy]cyclobutyl]amino]isoindoline- 1,3-dione

[00749] To a solution of benzyl N-[3-[3-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino] cyclobutoxy]propyl]-N-methyl-carbamate (0.80 g, 1.46 mmol) in DCM (10 mL) was added HBr/AcOH (1.46 mmol, 10 mL, 30% solution). The reaction mixture was stirred at 20 °C for 1 hour. On completion, the reaction mixture was dried by nitrogen. The residue was diluted with ACN/H_2O = 1/1 (100 mL) and lyophilizated to give the title compound (722 mg, 99% yield, HBr salt) as yellow solid. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 11.09 (s, 1H), 8.32 (s, 2H), 7.60 (dd, J = 7.2, 8.4 Hz, 1H), 7.09 (d, J = 7.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.68 - 6.25 (m, 1H), 5.06 (dd, J = 5.6, 12.8 Hz, 1H), 4.22 - 4.11 (m, 2H), 3.38 (t, J = 6.0 Hz, 2H), 3.04 - 2.80 (m, 3H), 2.63-2.55 (m, 4H), 2.54-2.52 (m, 1H), 2.44 - 2.33 (m, 2H), 2.29 - 2.18 (m, 2H), 2.12 - 1.97 (m, 1H), 1.90 - 1.76 (m, 2H).

[00750] 2-(2,6-Dioxo-3-piperidyl)-4-[2-(4-piperidyl)ethylamino]isoindoline-1,3-dione (Intermediate AVB)



[00751] Step 1 - Tert-butyl 4-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]piperidine- 1-carboxylate

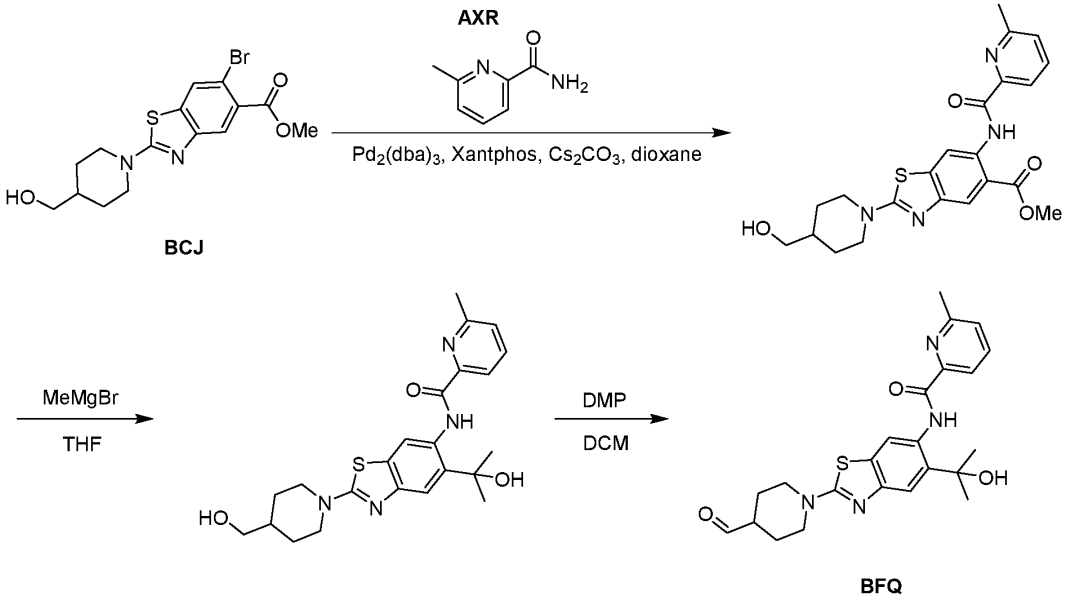
[00752] To a mixture of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (0.34 g, 1.23 mmol, Intermediate R) and tert-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (281 mg, 1.23 mmol, CAS# 146093-46-1) in DMSO (5 mL) was added DIPEA (318 mg, 2.46 mmol). The mixture was stirred at 130 °C for 2 hours. On completion, the reaction mixture was poured into the water (30 mL) and extracted with EA (2 X 20 mL). The combined organic phase was washed with brine (2 X 30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the residue. The residue was purified by column chromatography (SiO_2, PE: EA =10:1 to 3:1) to give the title compound (450 mg, 75% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.19 (d, J = 5.2 Hz, 1H), 4.10 (s, 1H), 3.35 - 3.28 (m, 2H), 2.96 - 2.79 (m, 2H), 2.78 - 2.65 (m, 4H), 1.83 - 1.65 (m, 4H), 1.65 - 1.52 (m, 4H), 1.46 (s, 9H), 1.18 (d, J = 7.2 Hz, 2H).

[00753] Step 2 - 2-(2,6-Dioxo-3-piperidyl)-4-[2-(4-piperidyl)ethylamino]isoindoline-1,3-dione

[00754] To a mixture of tert-butyl 4-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl] piperidine-1-carboxylate (0.12 g, 247 umol) in DCM (20 mL) was added HCl/dioxane (4 M, 185 uL). The reaction mixture was stirred at 20 °C for 0.5 hour. On completion, the reaction mixture

was concentrated *in vacuo* to give the title compound (95.0 mg, 91% yield) as a white solid. LC-MS (ESI^+) *m/z* 385.1 $(M+H)^+$.

[00755] N-[2-(4-formyl-1-piperidyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-methyl-pyridine-2-carboxamide (Intermediate BFQ)



[00756] Step 1 - Methyl 2-[4-(hydroxymethyl)-1-piperidyl]-6-[(6-methylpyridine-2-carbonyl)amino]-1,3- benzothiazole-5-carboxylate

[00757] To a solution of methyl 6-bromo-2-[4-(hydroxymethyl)-1-piperidyl]-1,3-benzothiazole-5-carboxylate (450 mg, 1.17 mmol, Intermediate BCJ) and 6-methylpyridine-2-carboxamide (159 mg, 1.17 mmol, Intermediate AXR) in dioxane (10 mL) was added Cs_2CO_3 (761 mg, 2.34 mmol), Xantphos (135 mg, 233 umol) and $Pd_2(dba)_3$ (106 mg, 116 umol), then the reaction mixture was stirred at 80 °C under N_2 for 12 hours. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 10/1 to 4/1) to give the title compound (360 mg, 70% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 9.20 (s, 1H), 8.01 - 7.94 (m, 3H), 7.55 (dd, J = 1.2, 6.8 Hz, 1H), 4.55 (t, J = 5.6 Hz, 1H), 4.09 - 4.00 (m, 2H), 3.96 (s, 3H), 3.30 - 3.25 (m, 2H), 3.21 - 3.12 (m, 2H), 2.64 (s, 3H), 1.84 - 1.75 (m, 2H), 1.72 - 1.65 (m, 1H), 1.28 - 1.20 (m, 2H).

[00758] Step 2 - N-[5-(1-hydroxy-1-methyl-ethyl)-2-[4-(hydroxymethyl)-1-piperidyl]-1,3-benzothiazol-6-yl] -6-methyl-pyridine-2-carboxamide

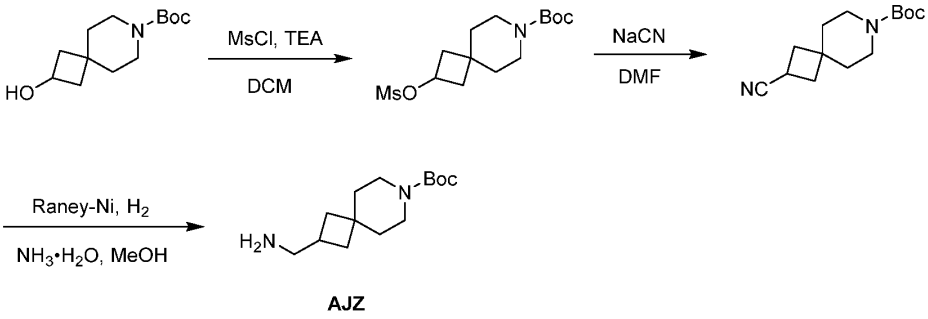
[00759] To a solution of methyl 2-[4-(hydroxymethyl)-1-piperidyl]-6-[(6-methylpyridine-2-carbonyl)amino]-1,3-benzothiazole-5-carboxylate (330 mg, 749 umol) in THF (20 mL) was added

MeMgBr (3 M, 1.25 mL) at 0 °C, then the reaction mixture was stirred at 0°C for 2 hours. On completion, the reaction was quenched with H_2O (15 mL), then extracted with DCM (2 X 30 mL). The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (80 mg, 24% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 8.78 (s, 1H), 7.99 - 7.88 (m, 2H), 7.50 (dd, J = 1.2, 7.2 Hz, 1H), 7.41 (s, 1H), 5.91 (s, 1H), 4.53 (t, J = 5.2 Hz, 1H), 4.08 - 3.96 (m, 2H), 3.30 - 3.25 (m, 2H), 3.17 - 3.09 (m, 2H), 2.60 (s, 3H), 1.82 - 1.74 (m, 2H), 1.70 - 1.64 (m, 1H), 1.59 (s, 6H), 1.28 - 1.16 (m, 2H); LC-MS (ESI$^+$) m/z 441.2(M+1)$^+$.

[00760] Step 3 - N-[2-(4-formyl-1-piperidyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-methyl- pyridine-2-carboxamide

[00761] To a solution of N-[5-(1-hydroxy-1-methyl-ethyl)-2-[4-(hydroxymethyl)-1-piperidyl]-1,3-benzothiazol -6-yl]-6-methyl-pyridine-2-carboxamide (75 mg, 170 umol) in DCM (4.0 mL) was added DMP (93.8 mg, 221 umol, 68.5 uL) and $NaHCO_3$ (71.5 mg, 851 umol), then the reaction mixture was stirred at 25 °C for 3 hour. On completion, the reaction mixture was quenched with $Na_2S_2O_3$ (10 mL) and extracted with DCM (2 X 20 mL). The combined organic phase was washed with aq. $NaHCO_3$ (15 mL) and brine (2 X 15 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (60 mg, 80% yield) as a yellow solid. LC-MS (ESI$^+$) m/z 439.2(M+1)$^+$.

[00762] Tert-butyl 2-(aminomethyl)-7-azaspiro[3.5]nonane-7-carboxylate (Intermediate AJZ)



AJZ

[00763] Step 1 - Tert-butyl 2-methylsulfonyloxy-7-azaspiro[3.5]nonane-7-carboxylate

[00764] To a solution of tert-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (2.00 g, 8.29 mmol, CAS# 240401-28-9) and TEA (2.10 g, 20.7 mmol) in DCM (30 mL) was added MsCl (1.14 g, 9.95 mmol) dropwise at 0 °C. Then the reaction mixture was stirred at 20 °C for 2 hrs. On completion, the mixture was quenched with water (50 mL), then extracted with DCM (2 X 50 mL). The organic layer was washed with citric acid (100 ml), brine (2 X 100 mL), dried with Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give the title compound (2.60 g, 98% yield) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (t, J = 7.2 Hz, 1H), 3.38 - 3.28 (m, 4H), 2.99 (s, 3H), 2.48 - 2.36 (m, 2H), 2.14 - 2.04 (m, 2H), 1.58 - 1.51

(m, 4H), 1.45 (s, 9H).

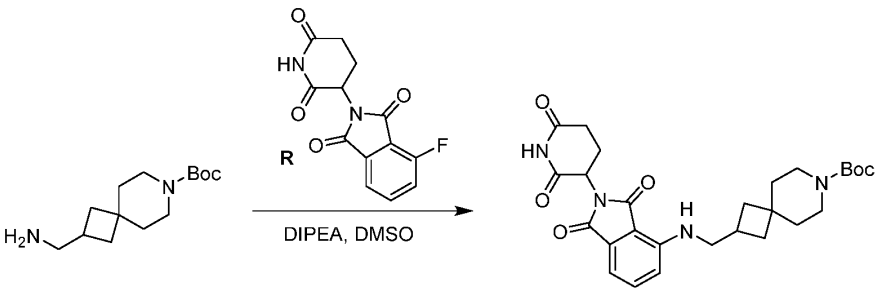
[00765] Step 2 - Tert-butyl 2-cyano-7-azaspiro[3.5]nonane-7-carboxylate

[00766] To a solution of tert-butyl 2-methylsulfonyloxy-7-azaspiro[3.5]nonane-7-carboxylate (2.60 g, 8.14 mmol) in DMF (20 mL) was added NaCN (598 mg, 12.2 mmol). The reaction mixture was stirred at 120 °C for 3 days. On completion, the reaction mixture was cooled to 25 °C, diluted with water (100 mL), then extracted with EA (2 X 100 mL). The organic layer was washed with brine (2 X 100 mL) and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the title compound (1.32 g, 65% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 - 3.29 (m, 4H), 3.13 - 3.02 (m, 1H), 2.30 - 2.14 (m, 4H), 1.66 - 1.62 (m, 2H), 1.58 - 1.53 (m, 2H), 1.45 (s, 9H).

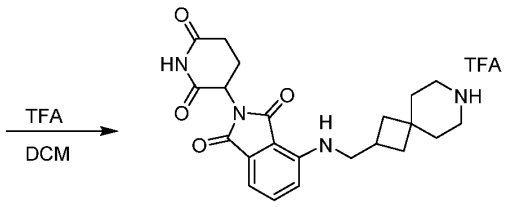
[00767] Step 3 - Tert-butyl 2-(aminomethyl)-7-azaspiro[3.5]nonane-7-carboxylate

[00768] To a solution of tert-butyl 2-cyano-7-azaspiro[3.5]nonane-7-carboxylate (200 mg, 799 umol) and NH_3•H_2O (0.2 mL) in MeOH (5 mL) was added Raney-Ni (30 mg). The reaction mixture was stirred at 20 °C for 16 hrs under H_2 (15 Psi) atmosphere. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound (200 mg, 98% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 - 3.32 (m, 2H), 3.30 - 3.23 (m, 2H), 2.70 (d, J = 7.2 Hz, 2H), 2.33 - 2.24 (m, 1H), 1.97 - 1.88 (m, 2H), 1.59 - 1.55 (m, 2H), 1.45 (s, 9H), 1.44 - 1.37 (m, 4H).

[00769] 4-(7-azaspiro[3.5]nonan-2-ylmethylamino)-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (Intermediate AJF)



AJZ



AJF

[00770] Step 1 - Tert-butyl 2-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]methyl]-7-

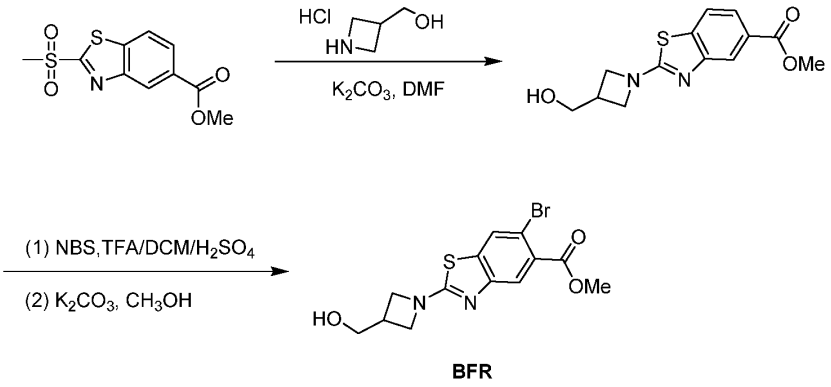
azaspiro [3.5]nonane-7-carboxylate

[00771] To a solution of tert-butyl 2-(aminomethyl)-7-azaspiro[3.5]nonane-7-carboxylate (200 mg, 786 umol, Intermediate AJZ) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (228 mg, 825 umol, Intermediate R) in DMSO (3 mL) was added DIPEA (254 mg, 1.97 mmol). The reaction mixture was stirred at 125 °C for 3 hrs. On completion, the reaction mixture was diluted with water (50 mL), then extracted with EA (50 mL). The organic layer was concentrated *in vacuo*. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (260 mg, 65% yield) as a yellow solid. LC-MS (ESI^+) *m/z* 511.3 $(M+H)^+$.

[00772] Step 2 - 4-(7-Azaspiro[3.5]nonan-2-ylmethylamino)-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione

[00773] To a solution of tert-butyl 2-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]methyl]-7- azaspiro[3.5]nonane-7-carboxylate (80.0 mg, 157 umol) in TFA (2 mL) was added DCM (2 mL). The reaction mixture was stirred at 20 °C for 2 hrs. On completion, the mixture was concentrated *in vacuo* to give the title compound (80 mg, 97% yield, TFA salt) as a yellow solid. LC-MS (ESI^+) *m/z* 411.2 $(M+H)^+$.

[00774] Methyl 6-bromo-2-[3-(hydroxymethyl)azetidin-1-yl]-1,3-benzothiazole-5-carboxylate (Intermediate BFR)



BFR

[00775] Step 1 - Methyl 2-[3-(hydroxymethyl)azetidin-1-yl]-1,3-benzothiazole-5-carboxylate

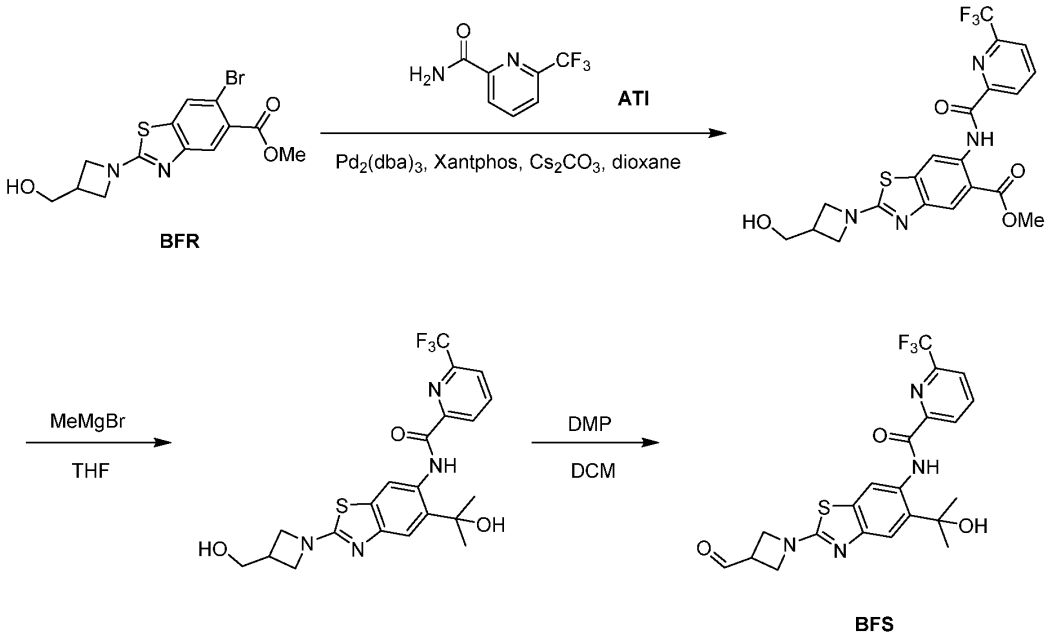
[00776] A mixture of methyl 2-methylsulfonyl-1,3-benzothiazole-5-carboxylate (2.00 g, 7.37 mmol, synthesized via Steps 1-3 of Intermediate BCJ), azetidin-3-ylmethanol (706 mg, 8.11 mmol, CAS# 928038-44-2) and K_2CO_3 (2.04 g, 14.7 mmol) in DMF (20 mL) was stirred at 60 °C for 2 hours. On completion, the reaction mixture was diluted with water (20 mL) and extracted with EA (3 X 20 mL). The combined organic layers was washed with brine (2 X 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.80 g, 87% yield) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 1.6 Hz, 1H), 7.70 (dd, J = 1.6, 8.2 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 4.21 (t, J = 8.4 Hz, 2H), 3.96 (dd, J =

5.2, 8.4 Hz, 2H), 3.85 (s, 3H), 3.83 (d, J = 6.0 Hz, 2H), 3.05 - 2.93 (m, 1H).

[00777] Step 2 - Methyl 6-bromo-2-[3-(hydroxymethyl)azetidin-1-yl]-1,3-benzothiazole-5-carboxylate

[00778] To a solution of methyl 2-[3-(hydroxymethyl)azetidin-1-yl]-1,3-benzothiazole-5-carboxylate (1.50 g, 5.39 mmol) in a mixed solution of DCM (6.0 mL), TFA (6.0 mL) and H_2SO_4 (3.0 mL) was added NBS (1.15 g, 6.47 mmol). The reaction mixture was stirred at 0 °C for 12 hours. On completion, a solution of K_2CO_3 (2.23 g, 16.17 mmol) in MeOH (1.0 mL) was added to the above mixture and stirred at 25 °C for 0.5 hour. After that, the reaction mixture was diluted with water (10 mL), then extracted with DCM (3X10 mL). The combined organic layer was washed with brine (3 X 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by silica gel chromatography (PE/EA/DCM = 1:1:0.1) to give the title compound (1.1 g, 57% yield) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.86 (s, 1H), 4.29 (t, J = 8.4 Hz, 2H), 4.03 (m, 3H), 3.94 (s, 3H), 3.91 (d, J = 5.6 Hz, 2H), 3.14 - 3.02 (m, 1H).

[00779] N-[2-(3-formylazetidin-1-yl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BFS)



BFS

[00780] Step 1 - Methyl 2-[3-(hydroxymethyl)azetidin-1-yl]-6-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino]-1,3-benzothiazole-5-carboxylate

[00781] A mixture of methyl 6-bromo-2-[3-(hydroxymethyl)azetidin-1-yl]-1,3-benzothiazole-5-carboxylate (400 mg, 1.12 mmol, Intermediate BFR), 6-(trifluoromethyl)pyridine-2-carboxamide (212 mg, 1.12 mmol, Intermediate ATI), Xantphos (129 mg, 223 umol), $Pd_2(dba)_3$ (102 mg, 111 umol) and Cs_2CO_3

(729 mg, 2.24 mmol) in dioxane (8.0 mL) was stirred at 80 °C for 12 hours. On completion, the reaction mixture was filtered and concentrated *in vacuo* to give a residue. The residue was purified by silica gel chromatography (PE/EA = 1:1) to give title compound (240 mg, 45% yield) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.89 (s, 1H), 9.20 (s, 1H), 8.42 (d, *J* = 5.0 Hz, 1H), 8.24 (s, 1H), 8.04 (t, *J* = 7.6 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 4.22 (t, *J* = 8.4 Hz, 2H), 4.00 - 3.93 (m, 5H), 3.83 (d, *J* = 6.4 Hz, 2H), 3.07 - 2.93 (m, 1H).

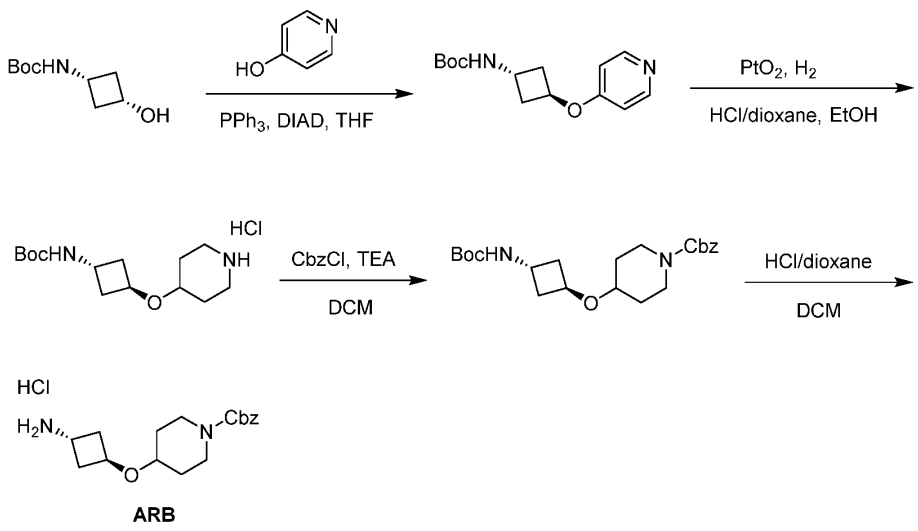
[00782] Step 2 - N-[2-[3-(hydroxymethyl)azetidin-1-yl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

[00783] To a solution of methyl 2-[3-(hydroxymethyl)azetidin-1-yl]-6-[[6-(trifluoromethyl)pyridine-2-carbonyl] amino]-1,3-benzothiazole-5-carboxylate (190 mg, 407 umol) in THF (2.0 mL) was added MeMgBr (3 M, 1.36 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was quenched with sat. aq. NH_4Cl (1.0 mL), diluted with water (5.0 mL), then extracted with EA (3 X 5.0 mL). The combined organic layer was washed with brine (2 X 5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (120 mg, 63% yield) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1H), 8.94 (s, 1H), 8.49 (d, *J* = 7.6 Hz, 1H), 8.11 (t, *J* = 7.6 Hz, 1H), 7.85 (*d*, *J* = 8.0 Hz, 1H), 7.61 (s, 1H), 5.31 (s, 2H), 4.28 (t, *J* = 8.0 Hz, 2H), 4.01 (dd, *J* = 5.6, 8.0 Hz, 2H), 3.91 (t, *J* = 5.2 Hz, 2H), 3.13 - 3.00 (m, 1H), 1.76 (s, 6H).

[00784] Step 3 - N-[2-(3-formylazetidin-1-yl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

[00785] To a solution of N-[2-[3-(hydroxymethyl)azetidin-1-yl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzo thiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (50.0 mg, 107 umol) in DCM (0.5 mL) was added DMP (59.1 mg, 139 umol). The reaction mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was quenched with saturated aq. $Na_2S_2O_3$ (1.0 mL) and saturated aq. $NaHCO_3$ (1.0 mL). The reaction mixture was diluted with water (5.0 mL), then extracted with DCM (3 X 5.0 mL). The combined organic layer was washed with brine (2 X 5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (40.0 mg, 80% yield) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.24 (s, 1H), 9.88 (d, *J* = 1.6 Hz, 1H), 8.89 (s, 1H), 8.42 (d, *J* = 7.6 Hz, 1H), 8.04 (t, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.55 (s, 1H), 4.37 - 4.24 (m, 4H), 3.66 - 3.55 (m, 1H), 1.69 (s, 6H).

[00786] Benzyl 4-(3-aminocyclobutoxy)piperidine-1-carboxylate (Intermediate ARB)



ARB

[00787] Step 1 - Tert-butyl N-[3-(4-pyridyloxy)cyclobutyl]carbamate

[00788] To a mixture of tert-butyl N-(3-hydroxycyclobutyl)carbamate (500 mg, 2.67 mmol, CAS# 154748-63-7) and pyridin-4-ol (253 mg, 2.67 mmol, CAS# 626-64-2) in THF (2.0 mL) was added PPh_3 (1.05 g, 4.01 mmol). Then DIAD (810 mg, 4.01 mmol) was added into the mixture at 0 °C. The mixture was stirred at 50 °C for 12 hours. On completion, the reaction was concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (365 mg, 51% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (br s, 2H), 7.31 (d, J = 6.8 Hz, 1H), 6.83 (d, J = 4.8 Hz, 2H), 4.92 - 4.84 (m, 1H), 4.09 (d, J = 6.8 Hz, 1H), 2.46 - 2.28 (m, 4H), 1.38 (s, 9H).

[00789] Step 2 - Tert-butyl N-[3-(4-piperidyloxy)cyclobutyl]carbamate

[00790] To a mixture of tert-butyl N-[3-(4-pyridyloxy)cyclobutyl]carbamate (450 mg, 1.70 mmol) in THF (30 mL) was added PtO_2 (386 mg, 1.70 mmol) and HCl/dioxane (4 M, 851 uL) under H_2 (50 psi). The mixture was stirred at 25 °C for 12 hours. On completion, the mixture was filtered and concentrated *in vacuo* to give the title compound (425 mg, 92% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 - 8.86 (m, 2H), 7.22 - 7.05 (m, 1H), 4.22 - 4.14 (m, 1H), 4.00 - 3.89 (m, 1H), 3.56 - 3.48 (m, 1H), 3.10 (s, 1H), 3.02 - 2.88 (m, 3H), 2.16 - 2.07 (m, 3H), 1.91 (d, J = 13.6 Hz, 1H), 1.72 - 1.59 (m, 3H), 1.37 (d, J = 1.1 Hz, 9H).

[00791] Step 3 - Benzyl 4-[3-(tert-butoxycarbonylamino)cyclobutoxy]piperidine-1-carboxylate

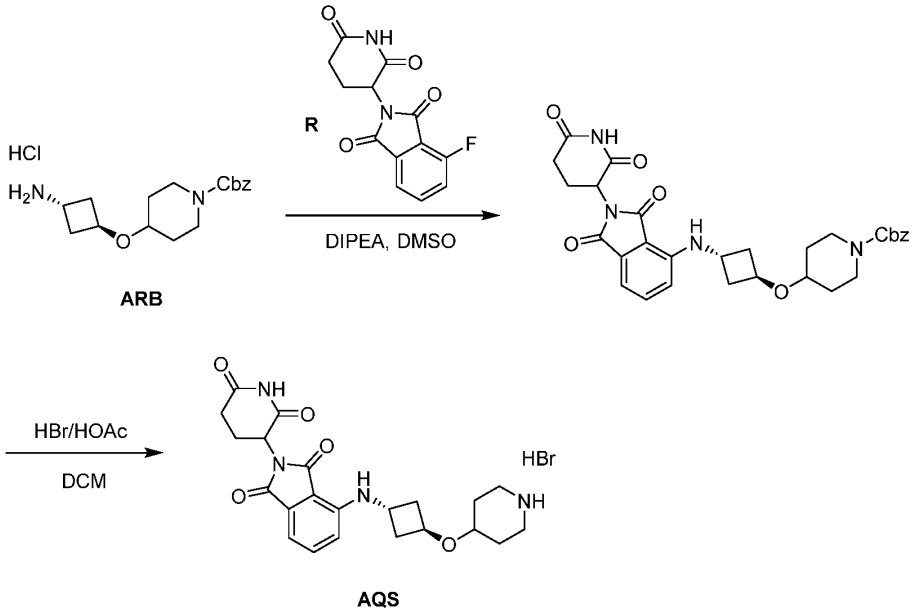
[00792] To a mixture of tert-butyl N-[3-(4-piperidyloxy)cyclobutyl]carbamate (345 mg, 1.28 mmol) in DCM (5 mL) was added TEA (387 mg, 3.83 mmol) and CbzCl (326 mg, 1.91 mmol). The mixture was stirred at 20 °C for 1 hour. On completion, the reaction mixture was concentrated to give the residue. The residue was purified by column chromatography (SiO_2, PE: EA = 2:1) to give the title compound (430 mg, 83% yield) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.27 (m, 5H), 5.13 (s, 2H), 4.79 - 4.53 (m,

1H), 4.27 - 4.07 (m, 2H), 3.89 - 3.79 (m, 2H), 3.53 - 3.35 (m, 1H), 3.17 (d, J = 26.4 Hz, 2H), 2.43 - 2.26 (m, 2H), 2.23 - 2.09 (m, 2H), 1.77 (s, 2H), 1.57 - 1.47 (m, 2H), 1.44 (s, 9H).

[00793] Step 4 - Benzyl 4-(3-aminocyclobutoxy)piperidine-1-carboxylate

[00794] To a mixture of benzyl 4-[3-(tert-butoxycarbonylamino)cyclobutoxy]piperidine-1-carboxylate (420 mg, 1.04 mmol) in DCM (20 mL) was added HCl/dioxane (4 M, 778 uL). The reaction mixture was stirred at 20 °C for 0.5 hour. On completion, the mixture was concentrated *in vacuo* to give the title compound (353 mg, 99% yield, HCl salt) as a yellow solid. LC-MS (ESI^+) m/z 305.2 $(M+H)^+$.

[00795] 2-(2,6-dioxo-3-piperidyl)-4-[[3-(4-piperidyloxy)cyclobutyl]amino]isoindoline-1,3-dione (Intermediate AQS)



[00796] Step 1 - Benzyl 4-[3-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]cyclobutoxy] piperidine-1-carboxylate

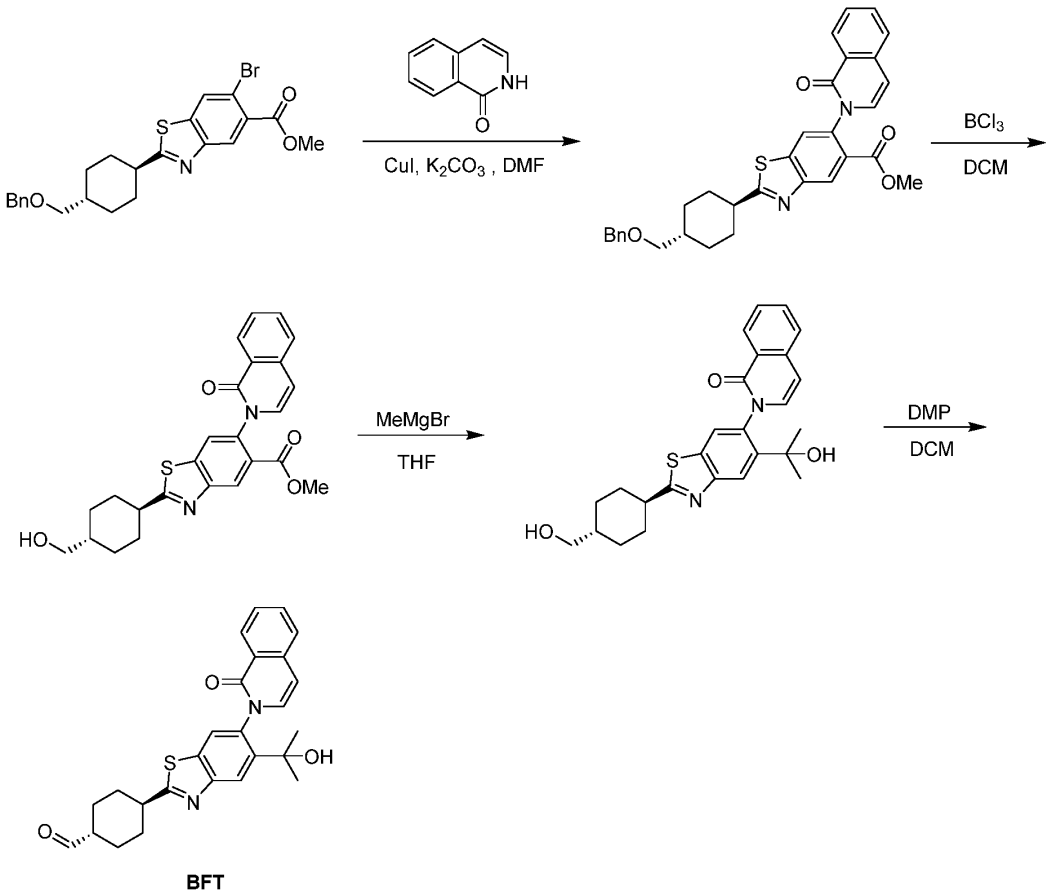
[00797] To a mixture of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (259 mg, 938 umol, Intermediate R) and benzyl 4-(3-aminocyclobutoxy)piperidine-1-carboxylate (320 mg, 938 umol, HCl salt, Intermediate ARB) in DMSO (10 mL) was added DIPEA (243 mg, 1.88 mmol). The mixture was stirred at 130 °C for 2 hours. On completion, the mixture was poured into water (30 mL) and the aqueous phase was extracted with ethyl acetate (2 X 20 mL). The combined organic phase was washed with brine (2 X 30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (220 mg, 41% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 7.67 - 7.53 (m, 1H), 7.43 - 7.27 (m, 5H), 7.09 (d, J

= 7.2 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 5.6 Hz, 1H), 5.13 - 5.01 (m, 3H), 4.33 (d, *J* = 6.0 Hz, 1H), 4.12 (d, *J* = 4.4 Hz, 1H), 3.80 - 3.70 (m, 2H), 3.54 - 3.44 (m, 1H), 3.20 - 3.03 (m, 2H), 2.97 - 2.84 (m, 1H), 2.70 - 2.54 (m, 2H), 2.42 - 2.32 (m, 2H), 2.31 - 2.21 (m, 2H), 2.08 - 1.99 (m, 1H), 1.86 - 1.73 (m, 2H), 1.42 - 1.29 (m, 2H).

[00798] Step 2 - 2-(2,6-Dioxo-3-piperidyl)-4-[[3-(4-piperidyloxy)cyclobutyl]amino]isoindoline-1,3-dione

[00799] To a mixture of benzyl 4-[3-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino] cyclobutoxy]piperidine-1-carboxylate (40 mg, 71.3 umol) in DCM (5 mL) was added HBr/HOAc (19.2 mg, 71.3 umol, 12.9 uL). The mixture was stirred at 20 °C for 0.5 hour. On completion, the mixture was concentrated *in vacuo* to give the title compound (32.0 mg, 100% yield) as brown oil. LC-MS (ESI^+) *m/z* 427.3 $(M+H)^+$.

[00800] 4-[5-(1-Hydroxy-1-methyl-ethyl)-6-(1-oxo-2-isoquinolyl)-1,3-benzothiazol-2-yl]cyclohexane carbaldehyde (Intermediate BFT)



BFT

[00801] Step 1 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-(1-oxo-2-isoquinolyl)-1,3-benzothiazole-5- carboxylate

[00802] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate (500 mg, 1.05 mmol, synthesized via Steps 1-3 of Intermediate BAW) and 2H-isoquinolin-1-one (183 mg, 1.26 mmol, CAS# 491-30-5) in DMF (8.0 mL) was added CuI (100 mg, 526 umol), and K_2CO_3 (291 mg, 2.11 mmol) at 25 °C, then the reaction mixture was stirred at 130 °C under N_2 for 12 hours. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 5/1) to give the title compound (200 mg, 35% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.30 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.79 - 7.70 (m, 2H), 7.58 - 7.52 (m, 1H), 7.50 - 7.44 (m, 1H), 6.74 (d, J = 7.6 Hz, 1H), 4.48 (s, 2H), 3.64 - 3.59 (m, 3H), 3.31 (s, 2H), 3.21 - 3.12 (m, 1H), 2.26 - 2.17 (m, 2H), 1.96 - 1.90 (m, 2H), 1.69 - 1.59 (m, 2H), 1.25 - 1.16 (m, 2H); LC-MS (ESI+) m/z 539.1 $(M+H)^+$.

[00803] Step 2 - Methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-(1-oxo-2-isoquinolyl)-1,3-benzothiazole-5- carboxylate

[00804] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-(1-oxo-2-isoquinolyl)-1,3-benzothiazole-5-carboxylate (130 mg, 241 umol) in DCM (2.5 mL) was added BCl_3 (1.0 M, 2.41 mL) at 0 °C. The mixture was stirred at 0-25 °C for 1 hour. On completion, the reaction mixture was diluted with H_2O (15 mL) and extracted with EA (3 X 5 mL). The combined organic layers were washed by brine (20 mL), dried over by Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give the title compound (100 mg, 92% yield) as yellow oil. LC-MS (ESI+) m/z 449.2 $(M+H)^+$.

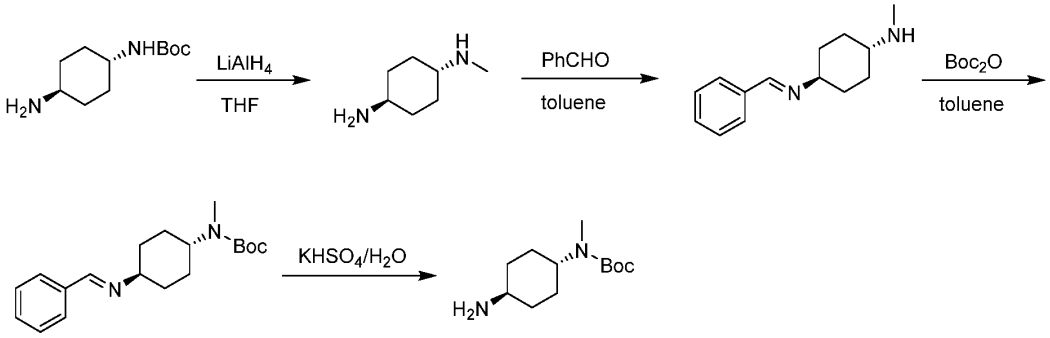
[00805] Step 3 - 2-[2-[4-(Hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6- yl]isoquinolin-1-one

[00806] To a solution of methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-(1-oxo-2-isoquinolyl)-1,3-benzothiazole-5-carboxylate (100 mg, 222 umol) in THF (2.0 mL) was added MeMgBr (3.0 M, 371 uL) at 0 °C. The mixture was stirred at 0-25 °C for 2 hours. On completion, the reaction mixture was quenched with sat. aq. NH_4Cl (2.0 mL) at 0 °C and diluted with H_2O (15 mL). The mixture was extracted with EA (3 X 15 mL). The combined organic layers were washed with brine (20 mL), dried over by Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225%FA)-ACN]; B%: 32%-59%, 9 min) to give the title compound (40.0 mg, 40% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.80 - 7.69 (m, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 5.13 (s, 1H), 4.50 - 4.31 (m, 1H), 3.29 (s, 2H), 3.14 - 3.04 (m, 1H), 2.19 (d, J = 12.4 Hz, 2H), 1.89 (d, J = 11.2 Hz, 2H), 1.67 - 1.49 (m, 3H), 1.36 (d, J = 9.2 Hz, 6H), 1.19 - 1.07 (m, 2H); LC-MS (ESI+) m/z 431.0 $(M-17)^+$.

[00807] Step 4 - 4-[5-(1-Hydroxy-1-methyl-ethyl)-6-(1-oxo-2-isoquinolyl)-1,3-benzothiazol-2-yl]cyclohexane carbaldehyde

[00808] To a solution of 2-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol -6-yl]isoquinolin-1-one (40.0 mg, 89.1 umol) in DCM (1.0 mL) was added DMP (49.1 mg, 115 umol) at 25 °C. The reaction mixture was stirred at 25°C for 2 hours. On completion, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (3.0 mL) and $NaHCO_3$ (3.0 mL), and then diluted with H_2O (15 mL). The mixture was extracted with DCM (3 X 5 mL). The combined organic layers were washed with brine (2 X 5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (39.0 mg, 97% yield) as a white solid. LC-MS (ESI+) m/z 429.3 $(M-17)^+$.

[00809] Tert-butyl N-(4-aminocyclohexyl)-N-methyl-carbamate (Intermediate AOZ)



AOZ

[00810] Step 1 - N4-methylcyclohexane-1,4-diamine

[00811] To a solution of tert-butyl N-(4-aminocyclohexyl)carbamate (15.0 g, 70.0 mmol, CAS# 177906-48-8) in THF (100 mL) was added $LiAlH_4$ (13.3 g, 350 mmol) at 0 °C. The mixture was stirred at 70 °C for 3 hours. On completion, the reaction was cooled to 20 °C, then it was quenched with H_2O (80 mL), filtered and the filtered cake was washed with EA (3 X 150 mL). The combined organic was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (6.90 g, 100% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.48 - 2.41 (m, 1H), 2.27 - 2.21 (m, 3H), 2.13 - 2.10 (m, 1H), 1.85 - 1.65 (m, 4H), 1.06 - 0.87 (m, 4H).

[00812] Step 2 - 4 -(Benzylideneamino)-N-methyl-cyclohexanamine

[00813] A solution of N4-methylcyclohexane-1,4-diamine (3.20 g, 20.0 mmol) and benzaldehyde (2.20 g, 21.0 mmol) in toluene (50 mL) was stirred at 120 °C for 16 hours. On completion, the reaction was concentrated *in vacuo* to give the title compound (4.00 g, 100% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.75 - 7.69 (m, 2H), 7.45 - 7.41 (m, 3H), 3.17 (br s, 1H), 2.30 (s, 4H), 1.98 - 1.91 (m, 2H), 1.71 - 1.63 (m, 2H), 1.60 - 1.47 (m, 2H), 1.16 - 1.05 (m, 2H).

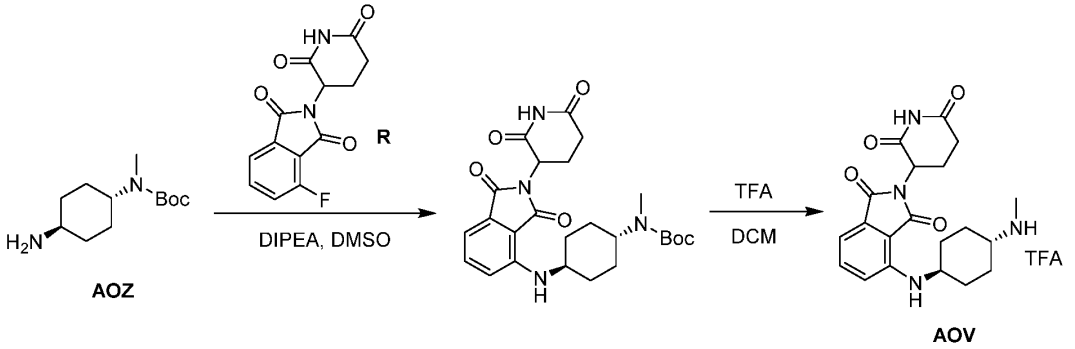
[00814] Step 3 - Tert-butyl N-[4-[(E)-benzylideneamino]cyclohexyl]-N-methyl-carbamate

[00815] To a solution of 4-[(E)-benzylideneamino]-N-methyl-cyclohexanamine (4.00 g, 18.5 mmol) in toluene (60 mL) was added $(Boc)_2O$ (4.80 g, 22.2 mmol, 5.1 mL). The mixture was stirred at 25 °C for 3 hours. On completion, the organic solvent was removed under vacuum to give the title compound (5.00 g, 90% yield) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.81 - 7.73 (m, 2H), 7.52 - 7.46 (m, 3H), 4.02 - 3.71 (m, 1H), 3.24 (d, J = 4.2 Hz, 1H), 2.74 (s, 3H), 1.83 - 1.74 (m, 2H), 1.73 - 1.62 (m, 6H), 1.46 (s, 9H).

[00816] Step 4 - Tert-butyl N-(4-aminocyclohexyl)-N-methyl-carbamate

[00817] A solution of $KHSO_4$ (7.5 g, 55.3 mmol) in H_2O (56 mL) was added to tert-butyl N-[4-[(E)-benzylideneamino]cyclohexyl]-N-methyl-carbamate (5 g, 15.8 mmol), and the reaction was stirred at 25 °C for 3 h. On completion, the reaction was extracted with MTBE (3 X 50 mL) and the aqueous phase was basified with NaOH (6 N) to pH=11, then it was extracted with DCM (5 X 50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum to give the title compound (3.00 g, 90% yield) as colorless oil. LC-MS (ESI^+) m/z 229.7 $(M+H)^+$.

[00818] 2-(2,6-dioxo-3-piperidyl)-4-[[4-(methylamino)cyclohexyl]amino]isoindoline-1,3- dione (Intermediate AOV)



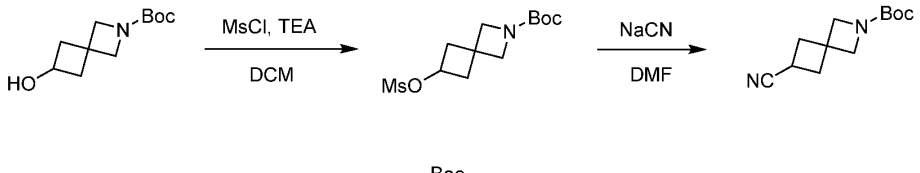
[00819] Step 1 - Tert-butyl N-[4-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]cyclohexyl]-N- methyl-carbamate

[00820] To a solution of tert-butyl N-(4-aminocyclohexyl)-N-methyl-carbamate (3.00 g, 13.1 mmol, Intermediate AOZ) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (3.60 g, 13.1 mmol, Intermediate R) in DMSO (30 mL) was added DIPEA (3.40 g, 26.3 mmol, 4.6 mL). The mixture was stirred at 130 °C for 2 hour. On completion, the crude product was purified by reversed-phase HPLC (0.1% FA condition) to give the title compound (3.40 g, 48% yield) as a yellow solid. LC-MS (ESI^+) m/z 485.5 $(M+H)^+$.

[00821] Step 2 - 2-(2,6-Dioxo-3-piperidyl)-4-[[4-(methylamino)cyclohexyl]amino]isoindoline-1,3-dione

[00822] To a solution of tert-butyl N-[4-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino] cyclohexyl]-N-methyl-carbamate (0.60 g, 1.2 mmol) in DCM (8 mL) was added TFA (6.20 g, 54.0 mmol, 4 mL). The mixture was stirred at 25 °C for 0.5 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (1.00 g, 100% yield, TFA) as yellow oil. LC-MS (ESI^+) m/z 384.9 $(M+H)^+$.

[00823] Tert-butyl 6-(aminomethyl)-2-azaspiro[3.3]heptane-2-carboxylate (Intermediate APA)



APA

[00824] Step 1 - Tert-butyl 6-((methylsulfonyl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate

[00825] To a solution of tert-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (2.5 g, 11.7 mmol, CAS# 1147557-97-8) in the DCM (20 mL) was added MsCl (2.01 g, 17.6 mmol) and TEA (3.56 g, 35.2 mmol, 4.89 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was quenched with water (20 mL) and extracted with EA (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (3.2 g, 94% yield) as yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (q, J = 7.2 Hz, 1H), 3.92 (d, J = 1.8 Hz, 4H), 2.98 (s, 3H), 2.72 - 2.65 (m, 2H), 2.51 - 2.42 (m, 2H), 1.42 (s, 9H).

[00826] Step 2 - Tert-butyl 6-cyano-2-azaspiro[3.3]heptane-2-carboxylate

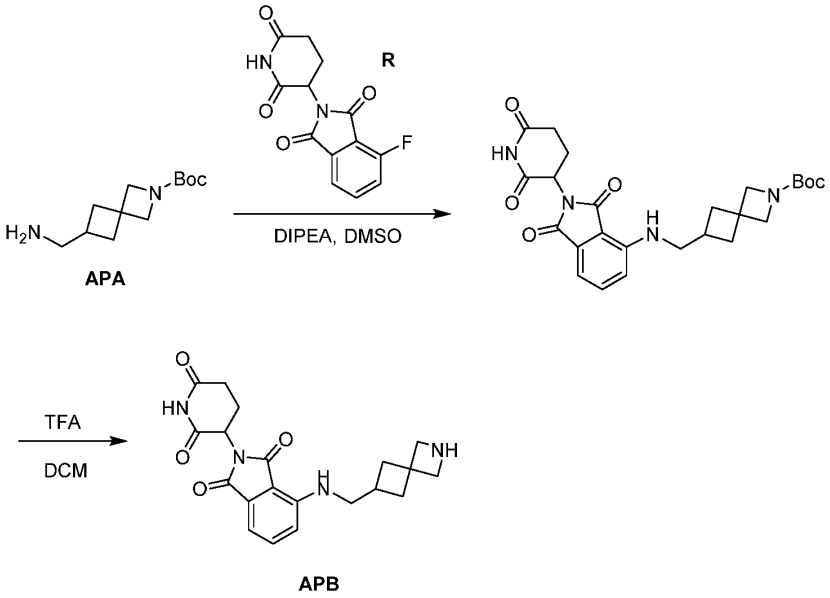
[00827] To a solution of tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate (3.2 g, 11.0 mmol) in the DMF (30 mL) was added NaCN (2.15 g, 43.9 mmol). The mixture was stirred at 100 °C for 18 hours. On completion, the reaction mixture was poured into water (200 mL) and extracted with EA (2 X 200 mL). The organic layer was washed with brine (200 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, PE: EA = 10:1 to 5:1) to give the title compound (1.6 g, 66% yield) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (d, J = 4.4 Hz, 4H), 3.00 (q, J = 8.3 Hz, 1H), 2.67 - 2.52 (m, 4H), 1.43 (s, 9H).

[00828] Step 3 - Tert-butyl 6-(aminomethyl)-2-azaspiro[3.3]heptane-2-carboxylate

[00829] To a solution of tert-butyl 6-cyano-2-azaspiro[3.3]heptane-2-carboxylate (0.8 g, 3.60 mmol) in the MeOH (5.0 mL) was added Raney-Ni (200 mg) and $NH_3·H_2O$ (1.01 g, 7.20 mmol). The reaction mixture was stirred at 25 °C for 4 hours under H_2 (50 Psi). On completion, the reaction mixture was filtered and concentrated *in vacuo* to give the title compound (800 mg, 98% yield) as colorless oil. ^1H NMR (400 MHz,

$CDCl_3$) δ 3.92 (s, 2H), 3.81 (s, 2H), 2.65 (d, J = 7.0 Hz, 2H), 2.30 - 2.22 (m, 2H), 2.22 - 2.11 (m, 1H), 1.85 - 1.77 (m, 2H), 1.43 (s, 9H).

[00830] 4-((2-Azaspiro[3.3]heptan-6-ylmethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Intermediate APB)



[00831] Step 1 - Tert-butyl 6-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)-2- azaspiro[3.3]heptane-2-carboxylate

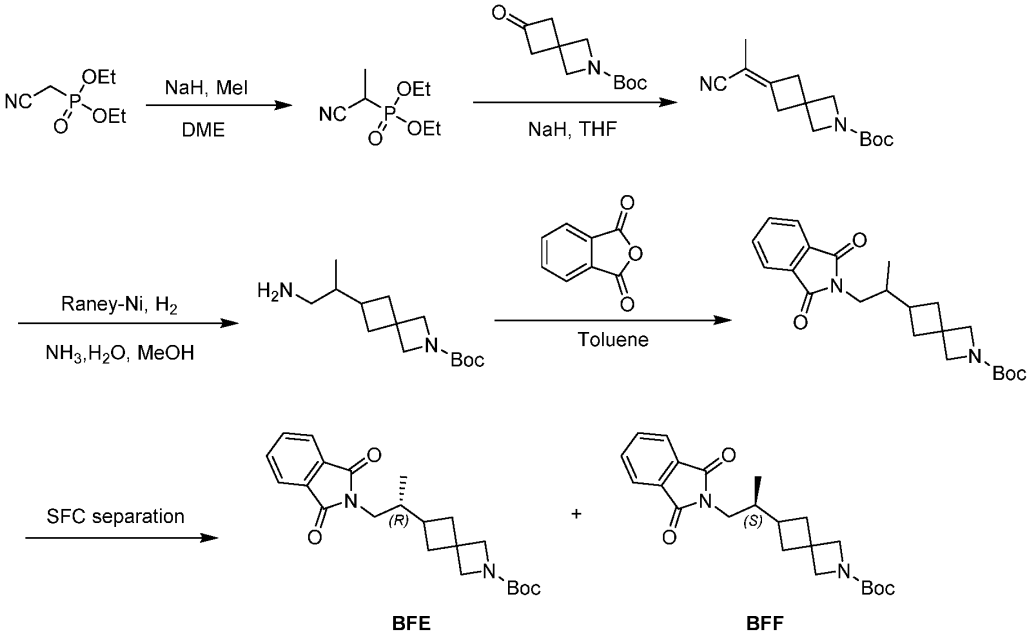
[00832] To a solution of tert-butyl 6-(aminomethyl)-2-azaspiro[3.3]heptane-2-carboxylate (100 mg, 442 umol, Intermediate APA) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (147 mg, 530 umol, Intermediate R) in the DMSO (2 mL) was added DIPEA (171 mg, 1.33 mmol, 231 uL). The mixture was stirred at 130 °C for 1 hour. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by reversed phase (FA condition) to give the title compound (140 mg, 66% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.43 (dd, J = 7.3, 8.4 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 6.11 (t, J = 5.4 Hz, 1H), 4.89 - 4.80 (m, 1H), 3.88 (s, 2H), 3.78 (s, 2H), 3.22 - 3.13 (m, 2H), 2.89 - 2.60 (m, 3H), 2.47 - 2.36 (m, 1H), 2.33 - 2.23 (m, 2H), 2.13 - 2.01 (m, 1H), 1.93 - 1.83 (m, 2H), 1.36 (s, 9H), 0.84 - 0.75 (m, 2H). LC-MS (ESI$^+$) m/z 483.3 $(M+H)^+$.

[00833] Step 2 - 4-((2-Azaspiro[3.3]heptan-6-ylmethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

[00834] To a solution of tert-butyl 6-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]methyl]-2- azaspiro[3.3]heptane-2-carboxylate (70 mg, 145 umol) in the DCM (2 mL) was added

TFA (1 mL). The mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (55 mg, 99% yield) as yellow solid. LC-MS (ESI^+) m/z 383.2 $(M+H)^+$.

[00835] Tert-butyl 6-[(1R)-2-(1,3-dioxoisoindolin-2-yl)-1-methyl-ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (Intermediate BFE) and tert-butyl 6-[(1S)-2-(1,3-dioxoisoindolin-2-yl)-1-methyl-ethyl]-2-azaspiro [3.3] heptanes-2-carboxylate (Intermediate BFF)



[00836] Step 1 - 2-Diethoxyphosphorylpropanenitrile

[00837] To a mixture of 2-diethoxyphosphorylacetonitrile (10.0 g, 56.45 mmol, CAS# 2537-48-6) in DMF (100 mL) was added NaH (2.71 g, 67.7 mmol, 60% dispersion in mineral oil) at 0 °C and the mixture was stirred for 1 hour. Then CH_3I (9.62 g, 67.7 mmol) was added dropwise into the mixture. The mixture was stirred at 20 °C for 2 hours. On completion, the mixture was poured into the water (300 mL). The aqueous phase was extracted with ethyl acetate (2 X 200 mL). The combined organic phase was washed with brine (2 X 200 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=3:1 to 0:1) to give the title compound (7.20 g, 66% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 - 4.19 (m, 4H), 3.05 - 2.82 (m, 1H), 1.57 - 1.51 (m, 3H), 1.41 - 1.34 (m, 6H).

[00838] Step 2 - Tert-butyl 6-(1-cyanoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate

[00839] To a mixture of 2-diethoxyphosphorylpropanenitrile (7.20 g, 37.7 mmol) in THF (80 mL) was added NaH (1.81 g, 45.2 mmol, 60% dispersion in mineral oil) at 0 °C and the mixture was stirred for 1

hour. Then tert-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (9.55 g, 45.2 mmol, CAS# 1147557-97-8) was added into the mixture and the mixture was stirred at 20 °C for 2 hours. On completion, the residue was poured into water (150 mL) and the aqueous phase was extracted with ethyl acetate (2 X 80 mL). The combined organic phase was washed with brine (2 X 80 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=3:1 to 0:1) to give the title compound (4.50 g, 48% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 - 3.87 (m, 4H), 3.00 (d, *J* = 1.6 Hz, 2H), 2.87 (s, 2H), 1.72 - 1.66 (m, 3H), 1.37 (s, 9H).

[00840] Step 3 - Tert-butyl 6-(2-amino-1-methyl-ethyl)-2-azaspiro[3.3]heptane-2-carboxylate

[00841] To a mixture of tert-butyl 6-(1-cyanoethylidene)-2-azaspiro[3.3]heptane-2-carboxylate (3.20 g, 12.9 mmol) in MeOH (50 mL) and $NH_3{\cdot}H_2O$ (5 mL) was added Raney-Ni (1.10 g, 12.89 mmol) under H_2 (50 psi) and the mixture was stirred at 30 °C for 12 hours. On completion, the mixture was filtered and concentrated *in vacuo* to give the title compound (2.70 g, 82% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 2H), 3.69 (s, 2H), 2.81 - 2.20 (m, 2H), 2.14 (d, *J* = 8.0 Hz, 2H), 1.87 - 1.69 (m, 3H), 1.36 (s, 9H), 1.30 - 1.18 (m, 2H), 1.08 (d, *J* = 15.2 Hz, 1H), 0.74 (d, *J* = 6.4 Hz, 3H).

[00842] Step 4 - Tert-butyl 6-[2-(1,3-dioxoisoindolin-2-yl)-1-methyl-ethyl]-2-azaspiro[3.3]heptane-2-carboxylate

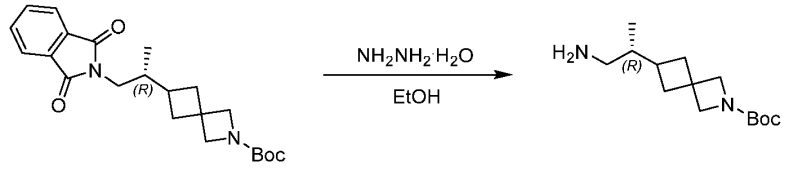
[00843] A solution of isobenzofuran-1,3-dione (1.89 g, 12.7 mmol) and tert-butyl 6-(2–amino-1-methyl-ethyl) -2-azaspiro[3.3]heptane-2-carboxylate (2.70 g, 10.6 mmol) in toluene (50 mL) was stirred at 110 °C for 12 hours. On completion, the mixture was concentrated *in vacuo* to give the residue. The residue was purified by column chromatography (SiO_2, PE: EA=10:1 to 3:1) to give the title compound (3.60 g, 77% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 2.8, 5.2 Hz, 2H), 7.74 (dd, *J* = 3.2, 5.2 Hz, 2H), 3.93 (s, 2H), 3.75 (s, 2H), 3.59 - 3.42 (m, 2H), 2.30 - 2.14 (m, 2H), 2.00 - 1.83 (m, 4H), 1.43 (s, 9H), 0.82 (d, *J* = 6.4 Hz, 3H).

[00844] Step 5 - Tert-butyl 6-[(1R)-2-(1,3-dioxoisoindolin-2-yl)-1-methyl-ethyl]-2-azaspiro[3.3]heptane-2- carboxylate and tert-butyl 6-[(1S)-2-(1,3-dioxoisoindolin-2-yl)-1-methyl-ethyl]-2-azaspiro [3.3] heptanes-2-carboxylate

[00845] Tert-butyl 6-[2-(1,3-dioxoisoindolin-2-yl)-1-methyl-ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (3.50 g, 9.10 mmol) was separated by SFC. The residue was purified by SFC (column: daicel chiralcel od (250mm*30mm, 10um); mobile phase: [0.1%NH_3H_2O.MEOH]; B%: %-%,0 min;0 min min) and (column: daicel chiralcel ad (250mm*30mm,10um); mobile phase: [0.1%NH_3H_2O ETOH]; B%: 25%-25%,5.4 min;130 minmin) to give tert-butyl 6-[(1R)-2-(1,3-dioxoisoindolin-2-yl)-1-methyl-ethyl]-2-azaspiro[3.3]heptane-2- carboxylate (1.20 g, 34% yield) and tert-butyl 6-[(1S)-2-(1,3-dioxoisoindolin-2-yl)-1-methyl-ethyl]-2-azaspiro [3.3] heptanes-2-carboxylate (1.20 g, 34% yield) as a white solid. Absolute

stereochemistry of the enantiomers were assigned arbitrarily.

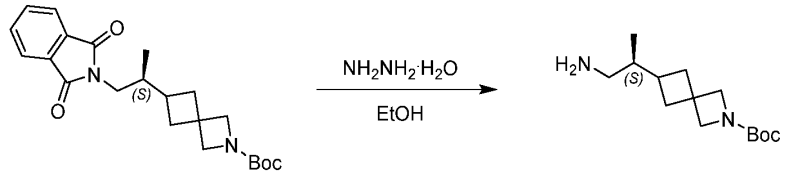
[00846] Tert-butyl 6-[(1R)-2-amino-1-methyl-ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (Intermediate BFG)



BFE BFG

[00847] To a mixture of tert-butyl 6-[(1R)-2-(1,3-dioxoisoindolin-2-yl)-1-methyl-ethyl]-2-azaspiro[3.3]heptane -2-carboxylate (600 mg, 1.56 mmol, Intermediate BFE) in EtOH (20 mL) was added $N_2H_4{\cdot}H_2O$ (208 mg, 3.12 mmol, 75% solution). The mixture was stirred at 80 °C for 2 hours. On completion, the mixture was cooled to 20 °C and filtered. The mother liquor was concentrated *in vacuo*. Then the DCM was added the residue and the mixture was stirred at 10 minutes. The mixture was filtered and the mother liquor was concentrated *in vacuo* to give the title compound (305 mg, 76% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 2H), 3.78 (s, 2H), 2.65 (dd, J = 4.4, 12.4 Hz, 1H), 2.36 (dd, J = 7.2, 12.4 Hz, 1H), 2.25 - 2.19 (m, 2H), 1.94 - 1.78 (m, 3H), 1.44 (s, 9H), 1.39 - 1.30 (m, 3H), 0.83 (d, J = 6.8 Hz, 3H).

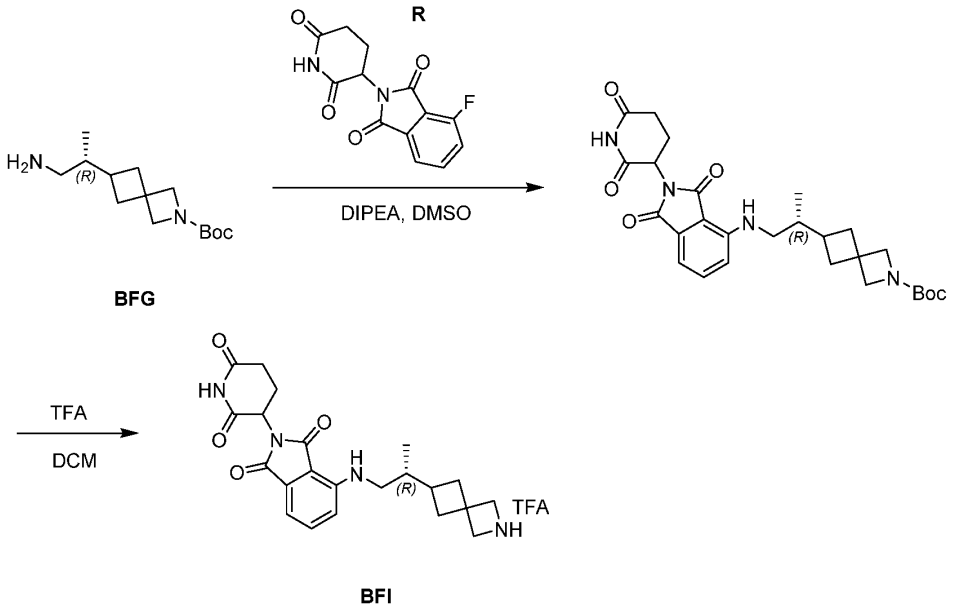
[00848] Tert-butyl 6-[(1S)-2-amino-1-methyl-ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (Intermediate BFH)



BFF BFH

[00849] To a mixture of tert-butyl 6-[(1S)-2-(1,3-dioxoisoindolin-2-yl)-1-methyl-ethyl]-2-azaspiro[3.3]heptane -2-carboxylate (500 mg, 1.30 mmol, Intermediate BFF) in EtOH (10 mL) was added $N_2H_4{\cdot}H_2O$ (132 mg, 26 uL, 98% solution). The reaction mixture was stirred at 80 °C for 12 hour. On completion, the reaction mixture was concentrated *in vacuo*. Then residue was diluted with DCM (20 mL) and filtered. The filtrate was concentrated in *vacuo* to give the title compound (300 mg, 90% yield) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 2H), 3.76 (s, 2H), 2.67 - 2.61 (m, 1H), 2.40 - 2.31 (m, 1H), 2.25 - 2.16 (m, 2H), 1.93 - 1.75 (m, 3H), 1.43 (s, 9H), 1.40 - 1.26 (m, 3H), 0.81 (d, J = 6.6 Hz, 3H).

[00850] 4-[[(2R)-2-(2-azaspiro[3.3]heptan-6-yl)propyl]amino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (Intermediate BFI)



[00851] Step 1 - Tert-butyl 6-[(1R)-2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]-1-methyl- ethyl]-2-azaspiro[3.3]heptane-2-carboxylate

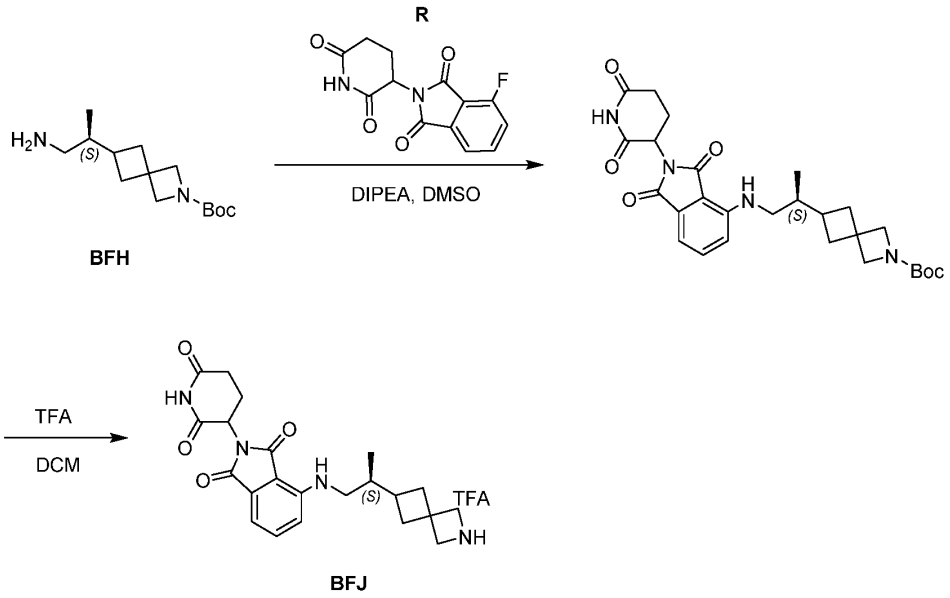
[00852] To a mixture of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (326 mg, 1.18 mmol, Intermediate R) and tert-butyl 6-[(1R)-2-amino-1-methyl-ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (300 mg, 1.18 mmol, Intermediate BFG) in DMSO (10 mL) was added DIPEA (304.85 mg, 2.36 mmol, 410.85 uL). The mixture was stirred at 130 °C for 2 hours. On completion, the residue was poured into water (30 mL) and the aqueous phase was extracted with ethyl acetate (2 X 20 mL). The combined organic phase was washed with brine (2 X 30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the residue. The residue was purified by reverse phase to give the title compound (425 mg, 70% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.50 (dd, J = 7.2, 8.4 Hz, 1H), 7.10 (d, J = 6.8 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.26 (t, J = 5.2 Hz, 1H), 4.92 (dd, J = 5.2, 12.0 Hz, 1H), 3.98 - 3.92 (m, 2H), 3.79 (s, 2H), 3.23 - 3.12 (m, 1H), 3.00 (dd, J = 6.4, 13.2 Hz, 1H), 2.94 - 2.87 (m, 1H), 2.85 - 2.69 (m, 2H), 2.37 - 2.22 (m, 2H), 2.19 - 2.11 (m, 1H), 1.98 - 1.85 (m, 2H), 1.68 (dd, J = 7.2, 14.8 Hz, 2H), 1.43 (s, 9H), 0.92 (d, J = 6.8 Hz, 3H).

[00853] Step 2 - 4-[[(2R)-2-(2-azaspiro[3.3]heptan-6-yl)propyl]amino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione

[00854] To a mixture of tert-butyl 6-[(1R)-2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl] amino]-1-methyl-ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (150 mg, 294 umol) in DCM (5 mL) was added TFA (67.0 mg, 587 umol) and the mixture was stirred at 20 °C for 0.5 hour. On completion, the

mixture was concentrated *in vacuo* to give the title compound (134 mg, 99% yield) as brown oil. LC-MS (ESI^+) *m/z* 411.2 $(M+H)^+$.

[00855] 4-[[(2S)-2-(2-azaspiro[3.3]heptan-6-yl)propyl]amino]-2-(2,6-dioxo-3-piperidyl)isoindoline -1,3-dione (Intermediate BFJ)



[00856] Step 1 - Tert-butyl 6-[(1S)-2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]-1-methyl -ethyl]-2-azaspiro[3.3]heptane-2-carboxylate

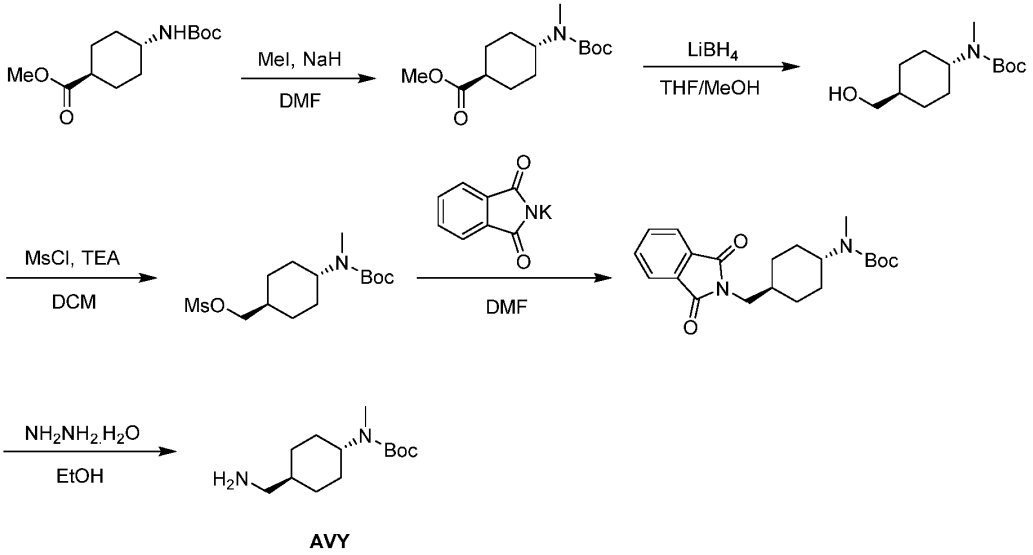
[00857] To a mixture of tert-butyl 6-[(1S)-2-amino-1-methyl-ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (300 mg, 1.18 mmol, Intermediate BFH) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (325 mg, 1.18 mmol, Intermediate R) in DMSO (3.0 mL) was added DIPEA (457 mg, 3.54 mmol, 616 uL). The reaction mixture was stirred at 130 °C for 2 hours. On completion, the reaction mixture was concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (480 mg, 79% yield) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ11.09 (s, 1H), 7.65 - 7.38 (m, 1H), 7.13 - 6.94 (m, 2H), 6.47 (t, J = 6.0 Hz, 1H), 5.09 - 5.02 (m, 1H), 3.84 (s, 2H), 3.68 (s, 2H), 3.23 - 3.13 (m, 1H), 3.09 - 2.98 (m, 1H), 2.94 - 2.81 (m, 1H), 2.63 - 2.52 (m, 2H), 2.26 - 2.15 (m, 2H), 2.06 - 1.98 (m, 1H), 1.96 - 1.87 (m, 2H), 1.86 - 1.76 (m, 1H), 1.70 - 1.59 (m, 1H), 1.35 (s, 9H), 0.80 (d, J = 6.4 Hz, 3H).

[00858] Step 2 - 4-[[(2S)-2-(2-azaspiro[3.3]heptan-6-yl)propyl]amino]-2-(2,6-dioxo-3-piperidyl)isoindoline -1,3-dione

[00859] To a mixture of tert-butyl 6-[(1S)-2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]-1- methyl-ethyl]-2-azaspiro[3.3]heptane-2-carboxylate (120 mg, 235 umol) in DCM (2.0 mL)

was added TFA (1.85 g, 16.2 mmol, 1.20 mL). The reaction mixture was stirred at 25 °C for 0.5 hour. On completion, the reaction mixture was concentrated *in vacuo* to give title compound (120 mg, 97% yield, TFA salt) as red oil. LC-MS (ESI^+) *m/z* 411.2 $(M+H)^+$.

[00860] Tert-butyl ((1r,4r)-4-(aminomethyl)cyclohexyl)(methyl)carbamate (Intermediate AVY)



AVY

[00861] Step 1 - (1R,4r)-methyl 4-((tert-butoxycarbonyl)(methyl)amino)cyclohexanecarboxylate

[00862] To a solution of methyl 4-(tert-butoxycarbonylamino)cyclohexanecarboxylate (2.00 g, 7.77 mmol, CAS# 146307-51-9) in DMF (20 mL) was added NaH (373 mg, 9.33 mmol, 60% dispersion in mineral oil) under 0°C for 0.5 hr. Then CH_3I (1.32 g, 9.33 mmol, 581 uL) was added to the reaction mixture and the mixture was stirred at 25°C for 2 hrs. On completion, the reaction mixture was diluted with 100 mL H_2O and extracted with EA (3 X 50 mL). The combined organic layers were washed with NaCl (50 mL X 2), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to give the title compound (1.80 g, 85% yield) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 3.61 - 3.54 (m, 3H), 3.17 (d, J = 5.3 Hz, 1H), 2.65 (s, 3H), 2.31 - 2.15 (m, 1H), 2.01 - 1.88 (m, 2H), 1.62 - 1.31 (m, 13H).

[00863] Step 2 - Tert-butyl ((1r,4r)-4-(hydroxymethyl)cyclohexyl)(methyl)carbamate

[00864] To a solution of methyl 4-[tert-butoxycarbonyl(methyl)amino]cyclohexanecarboxylate (800 mg, 2.95 mmol) in THF (12 mL) and MeOH (3 mL) was cooled to 0°C and slowly added $LiBH_4$ (193 mg, 8.84 mmol) under N_2 atmosphere. After that, the reaction mixture was warmed to 50 °C and stirred for 2 hours. On completion, the reaction mixture was diluted with 100 mL H_2O and extracted with EA 150 mL (50 mL X 3). The combined organic layers were washed with NaCl 100 mL (50mL X 2), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.00 g, 70% purity, 97% yield) as a yellow

solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.39 (t, J = 5.2 Hz, 1H), 4.11 - 3.98 (m, 1H), 3.20 (t, J = 5.6 Hz, 2H), 2.65 (s, 3H), 1.77 (d, J = 11.2 Hz, 2H), 1.65 - 1.40 (m, 4H), 1.38 (s, 9H), 1.17 (t, J = 7.2 Hz, 3H).

[00865] Step 3 - ((1R,4r)-4-((tert-butoxycarbonyl)(methyl)amino)cyclohexyl)methyl methanesulfonate

[00866] To a solution of tert-butyl N-[4-(hydroxymethyl)cyclohexyl]-N-methyl-carbamate (0.90 g, 3.70 mmol) in DCM (10 mL) was added MsCl (847 mg, 7.40 mmol, 572 uL) and TEA (1.12 g, 11.10 mmol, 1.54 mL). The mixture was stirred at 0 °C for 2 hours. On completion, the reaction mixture was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM (50 mL X 3). The combined organic layers were washed with NaCl (50 mL X 2), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.00 g, 84% yield) as a yellow oil. The crude product was used to the next step directly without further purification.

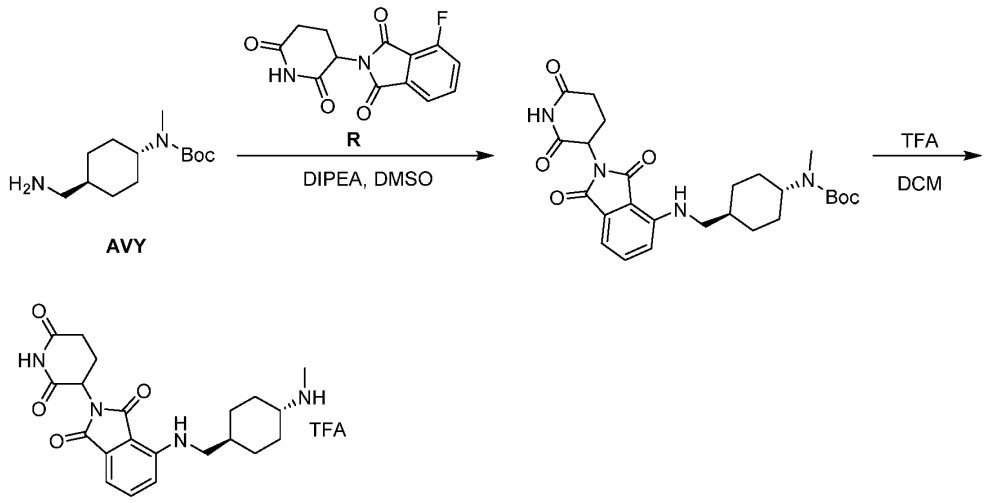
[00867] Step 4 - Tert-butyl ((1r,4r)-4-((1,3-dioxoisoindolin-2-yl)methyl)cyclohexyl)(methyl)carbamate

[00868] To a solution of [4-[tert-butoxycarbonyl(methyl)amino]cyclohexyl]methyl methanesulfonate (1.00 g, 3.11 mmol) in DMF (10 mL) was added (1,3-dioxoisoindolin-2-yl)potassium (1.15 g, 6.22 mmol). The mixture was stirred at 40 °C for 16 hrs. On completion, the reaction mixture was diluted with 100 mL H_2O and extracted with EA (50mL X 3). The combined organic layers were washed with NaCl (50 mL X 2), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to give the title compound (1.00 g, 84% purity, 72% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 - 7.81 (m, 4H), 3.85 - 3.64 (m, 1H), 3.43 (d, J = 7.2 Hz, 2H), 2.62 (s, 3H), 1.71 (d, J = 13.2 Hz, 2H), 1.63 (dd, J = 3.6, 7.6 Hz, 1H), 1.58 - 1.42 (m, 3H), 1.38 (s, 9H), 1.26 - 1.15 (m, 1H), 1.12 - 0.99 (m, 2H).

[00869] Step 5 - Tert-butyl ((1r,4r)-4-(aminomethyl)cyclohexyl)(methyl)carbamate

[00870] To a solution of tert-butyl N-[4-[(1,3-dioxoisoindolin-2-yl)methyl]cyclohexyl]-N-methyl-carbamate (1.00 g, 2.26 mmol) in EtOH (10 mL) was added $NH_2NH_2{\cdot}H_2O$ (266 mg, 4.51 mmol, 258 uL, 85% solution). The mixture was stirred at 60 °C for 2 hrs. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound (800 mg, 80% purity, 98% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.16 (s, 2H), 3.44 (q, J = 7.2 Hz, 1H), 2.66 - 2.62 (m, 3H), 2.42 (d, J = 6.4 Hz, 2H), 1.92 - 1.68 (m, 2H), 1.54 (s, 2H), 1.46 - 1.39 (m, 2H), 1.38 (s, 9H), 1.27 - 1.16 (m, 1H), 0.98 - 0.84 (m, 2H).

[00871] 2-(2,6-Dioxopiperidin-3-yl)-4-((((1r,4r)-4-(methylamino)cyclohexyl)methyl)amino) isoindoline-1,3-dione (Intermediate AVZ)



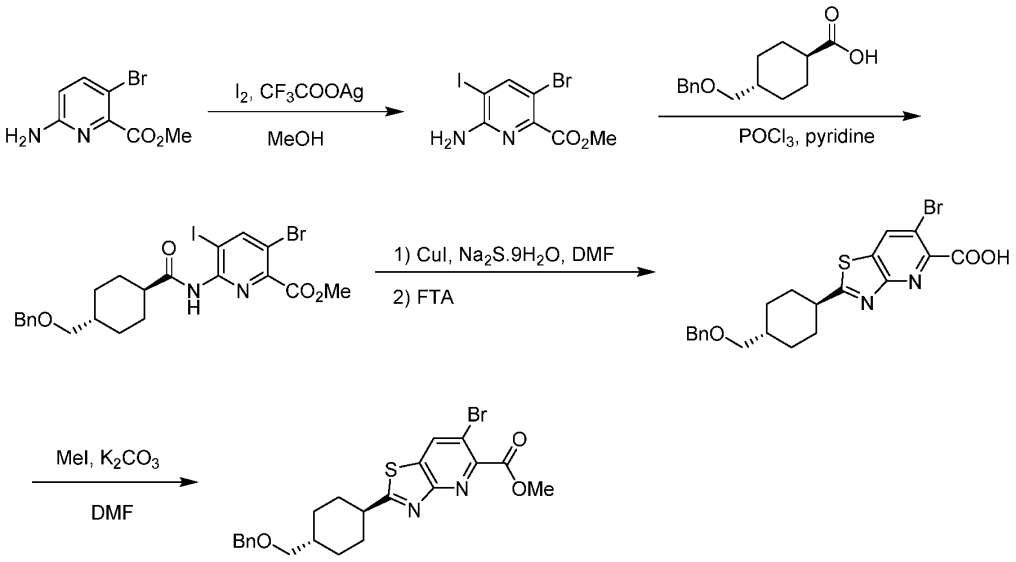
[00872] Step 1 - Tert-butyl ((1r,4r)-4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl) cyclohexyl)(methyl)carbamate

[00873] To a solution of tert-butyl N-[4-(aminomethyl)cyclohexyl]-N-methyl-carbamate (750 mg, 3.09 mmol, Intermediate AVY) in DMSO (10 mL) was added 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (1.71 g, 6.19 mmol, Intermediate R) and DIPEA (1.20 g, 9.28 mmol, 1.62 mL). The mixture was stirred at 130 °C for 0.5 hr. On completion, the reaction mixture was filtered and concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (FA condition) to give the title compound (300 mg, 18% yield, 95% purity) as yellow oil. LC-MS (ESI^+) *m/z* 499.4 $(M+H)^+$.

[00874] Step 2 - 2-(2,6-Dioxopiperidin-3-yl)-4-((((1r,4r)-4-(methylamino)cyclohexyl)methyl)amino) isoindoline-1,3-dione

[00875] To a solution of tert-butyl N-[4-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]methyl] cyclohexyl]-N-methyl-carbamate (150 mg, 286 umol) in DCM (1 mL) was added TFA (0.5 mL). The mixture was stirred at 25 °C for 0.5 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (150 mg, TFA, 96% yield) as yellow oil. LC-MS (ESI^+) *m/z* 399.4 $(M+H)^+$.

[00876] Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-thiazolo[4,5-b]pyridine-5-carboxylate (Intermediate BGV)



BGV

[00877] Step 1 - Methyl 6-amino-3-bromo-5-iodo-pyridine-2-carboxylate

[00878] To a mixture of methyl 6-amino-3-bromo-pyridine-2-carboxylate (12.8 g, 55.4 mmol, CAS# 36052- 26-3) in MeOH (200 mL) was added (2,2,2-trifluoroacetyl)oxysilver (30.5 g, 138 mmol) and I_2 (35.1 g, 138 mmol) at 25 °C under N_2. The mixture was stirred at 40 °C for 24 hours. On completion, the reaction mixture was quenched with saturated aqueous Na_2SO_3 (30 mL) at 25°C, and then extracted with EA (3 X 60 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 5/1) to give the title compound (2.0 g, 10% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 5.20 (s, 2H), 3.96 (s, 3H).

[00879] Step 2 - Methyl 6-[[4-(benzyloxymethyl)cyclohexanecarbonyl]amino]-3-bromo-5-iodo-pyridine- 2-carboxylate

[00880] To a solution of methyl 6-amino-3-bromo-5-iodo-pyridine-2-carboxylate (2.0 g, 5.60 mmol) and 4-(benzyloxymethyl)cyclohexanecarboxylic acid (1.39 g, 5.60 mmol, synthesized via Steps 1-3 of Intermediate BAU) in pyridine (20 mL) was added $POCl_3$ (1.29 g, 8.40 mmol, 781 uL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours. On completion, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to give a residue. The residue was dissolved in EA (40 mL) and washed consecutively with a saturated aqueous Na_2SO_3 (3 X 30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (1.0 g, 30% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.75 (s, 1H), 7.41 - 7.22 (m, 5H), 4.45 (s, 2H), 3.93

- 3.86 (m, 3H), 3.27 (d, J = 6.4 Hz, 2H), 2.37 - 2.28 (m, 1H), 1.96 - 1.87 (m, 2H), 1.86 - 1.78 (m, 2H), 1.64 - 1.52 (m, 1H), 1.51 - 1.38 (m, 2H), 1.07 - 1.92 (m, 2H); LC-MS (ESI^+) m/z 587.1 $(M+1)^+$.

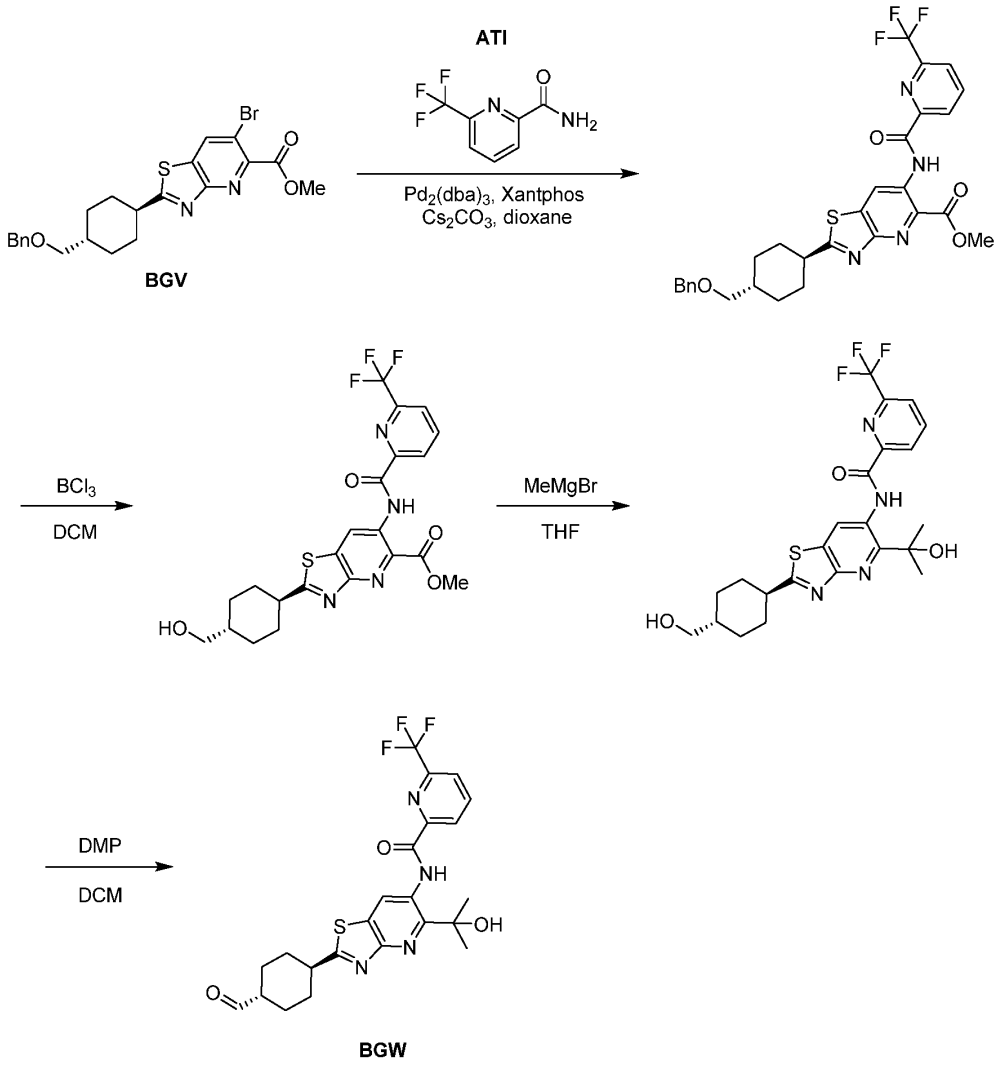
[00881] Step 3 - 2-[4-(Benzyloxymethyl)cyclohexyl]-6-bromo-thiazolo[4,5-b]pyridine-5-carboxylic acid

[00882] To a solution of methyl 6-[[4-(benzyloxymethyl)cyclohexanecarbonyl]amino]-3-bromo-5-iodo- pyridine-2-carboxylate (1.0 g, 1.70 mmol) in DMF (15 mL) was added CuI (64.8 mg, 340 umol) and $Na_2S{\cdot}9H_2O$ (1.64 g, 6.81 mmol). The mixture was stirred at 80 °C under N_2 for 12 hours. Then the mixture was cooled down to 25 °C and TFA (1.94 g, 17.0 mmol, 1.26 mL) was added. The mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was quenched with H_2O (60 mL), then extracted with EA (2 X 100 mL). The combined organic phase was concentrated *in vacuo* to give the title compound (780 mg, 52% yield) as a yellow solid. LC-MS (ESI^+) m/z 463.1$(M+1)^+$.

[00883] Step 4 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-thiazolo[4,5-b]pyridine-5-carboxylate

[00884] To a solution of 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-thiazolo[4,5-b]pyridine-5-carboxylic acid (780 mg, 1.69 mmol) and K_2CO_3 (467 mg, 3.38 mmol) in DMF (10 mL) was added MeI (479 mg, 3.38 mmol) at 0 °C, then the reaction mixture was stirred at 25 °C for 3 hours. On completion, the mixture was filtered, and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) the title compound (390 mg, 48% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.41 - 7.23 (m, 5H), 4.47 (s, 2H), 3.94 (s, 3H), 3.31 (d, J = 6.0 Hz, 2H), 3.22 - 3.11 (m, 1H), 2.24 - 2.14 (m, 2H), 1.95 - 1.86 (m, 2H), 1.75 - 1.53 (m, 3H), 1.12 - 1.26 (m, 2H); LC-MS (ESI^+) m/z 475.1 $(M+1)^+$.

[00885] N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)thiazolo[4,5-b]pyridin-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BGW)



[00886] Step 1 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[[6-(trifluoromethyl)pyridine-2-carbonyl] amino]thiazolo[4,5-b]pyridine-5-carboxylate

[00887] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-thiazolo[4,5-b]pyridine-5-carboxylate (390 mg, 820 umol, Intermediate BGV) and 6-(trifluoromethyl)pyridine-2-carboxamide (155 mg, 820 umol, Intermediate ATI) in dioxane (10 mL) was addeed $Pd_2(dba)_3$ (75.1 mg, 82.0 umol), Cs_2CO_3 (534 mg, 1.64 mmol) and Xantphos (94.9 mg, 164 umol), then the reaction mixture was stirred at 80 °C for 12 hours. On completion, the mixture was filtered, and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (420 mg, 87% yield) as a yellow solid. LC-MS (ESI^+) *m/z* 585.2 $(M+1)^+$.

[00888] Step 2 - Methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-[[6-(trifluoromethyl)pyridine-2-

carbonyl]amino] thiazolo[4,5-b]pyridine-5-carboxylate

[00889] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino]thiazolo[4,5-b]pyridine-5-carboxylate (300 mg, 513 umol) in DCM (2.0 mL) was added BCl_3 (1 M, 5.13 mL), then the reaction mixture was stirred at 15 °C for 2 hours. On completion, the reaction mixture was quenched with H_2O (10 mL), then extracted with DCM (2 X 20 mL). The combined organic phase was concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (65 mg, 25% yield) as a light yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.72 (s, 1H), 9.83 (s, 1H), 8.56 - 8.46 (m, 1H), 8.46 - 8.39 (m, 1H), 8.29 - 8.23 (m, 1H), 4.59 - 4.33 (m, 1H), 3.99 (s, 3H), 3.28 (d, J = 6.0 Hz, 2H), 3.18 - 3.08 (m, 1H), 2.26 - 2.16 (m, 2H), 1.95 - 1.82 (m, 2H), 1.67 - 1.53 (m, 2H), 1.51 - 1.42 (m, 1H), 1.19 - 1.07 (m, 2H); LC-MS (ESI^+) *m/z* 495.2 $(M+1)^+$.

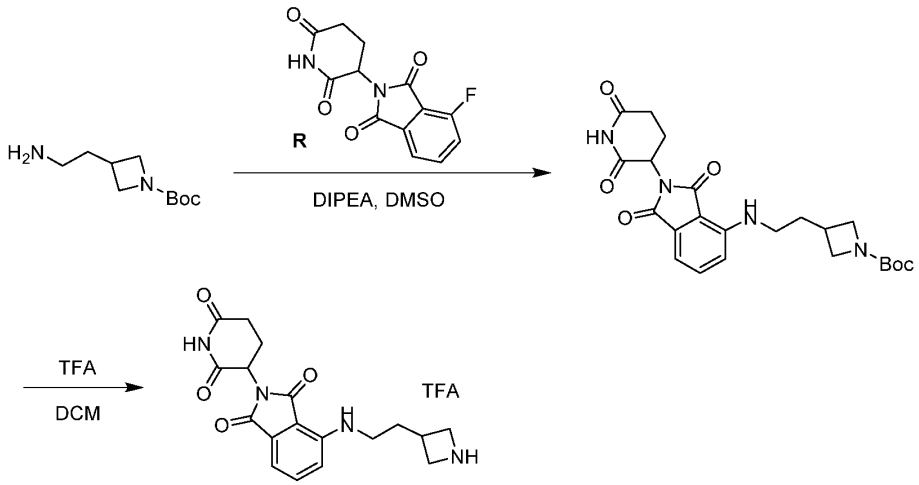
[00890] Step 3 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)thiazolo[4,5-b]pyridin-6- yl]-6-(trifluoromethyl)pyridine-2-carboxamide

[00891] To a solution of methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-[[6-(trifluoromethyl)pyridine-2-carbonyl] amino]thiazolo[4,5-b]pyridine-5-carboxylate (55 mg, 111 umol) in THF (1.0 mL) was added MeMgBr (3 M, 370 uL) at 0 °C, then the reaction mixture was stirred at 0 °C for 2 hours. On completion, the reaction mixture was quenched with H_2O (20 mL) and then extracted with DCM (2 X 40 mL). The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give the title compound (40 mg, 72% yield) as a white solid. LC-MS (ESI^+) *m/z* 495.2 $(M+1)^+$.

[00892] Step 4 - N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)thiazolo[4,5-b]pyridin-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

[00893] To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)thiazolo[4,5-b] pyridin-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (35 mg, 70.7 umol) in DCM (1.0 mL) was added DMP (39.0 mg, 92.0 umol) and $NaHCO_3$ (29.7 mg, 353 umol), then the reaction mixture was stirred at 20 °C for 3 hours. On completion, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL) and extracted with DCM (2 X 20 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (2 X 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (30 mg, 86% yield) as a yellow solid. LC-MS (ESI^+) *m/z* 493.2 $(M+1)^+$.

[00894] 4-[2-(Azetidin-3-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (Intermediate BGX)



BGX

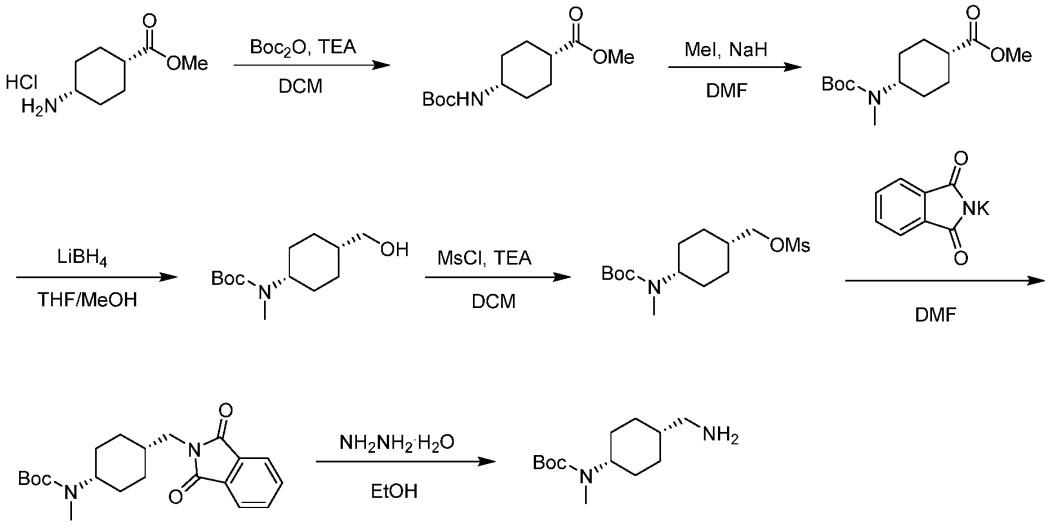
[00895] Step 1 - Tert-butyl 3-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]azetidine- 1-carboxylate

[00896] To a solution of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (300 mg, 1.09 mmol, Intermediate R) and tert-butyl 3-(2-aminoethyl)azetidine-1-carboxylate (217 mg, 1.09 mmol, CAS# 898271-20-0) in DMSO (5 mL) was added DIPEA (421 mg, 3.26 mmol, 567 uL). The reaction mixture was stirred at 130 °C for 3 hrs. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (300 mg, 60% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.58 (dd, J = 7.2, 8.4 Hz, 1H), 7.11 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 6.8 Hz, 1H), 6.59 (t, J = 6.0 Hz, 1H), 5.05 (dd, J = 5.2, 12.8 Hz, 1H), 4.01 - 3.83 (m, 2H), 3.57 - 3.46 (m, 2H), 3.30 - 3.25 (m, 2H), 2.95 - 2.80 (m, 1H), 2.64 - 2.51 (m, 3H), 2.07 - 1.97 (m, 1H), 1.83 (q, J = 7.3 Hz, 2H), 1.36 (s, 9H); LC-MS (ESI$^+$) m/z 357.1 $(M+H-100)^+$.

[00897] Step 2 - 4-[2-(Azetidin-3-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione

[00898] To a solution of tert-butyl 3-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl] azetidine-1-carboxylate (50.0 mg, 109 umol) in DCM (2 mL) was added TFA (770 mg, 6.75 mmol, 0.5 mL). The reaction mixture was stirred at 20 °C for 30 min. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (500 mg, 97.0% yield, TFA salt) as a yellow solid. LC-MS (ESI$^+$) m/z 357.2$(M+H)^+$.

[00899] Tert-butyl ((1s,4s)-4-(aminomethyl)cyclohexyl)(methyl)carbamate (Intermediate AYZ)



AYZ

[00900] Step 1 - (1s,4s)-Methyl 4-((tert-butoxycarbonyl)amino)cyclohexanecarboxylate

[00901] To a solution of methyl 4-aminocyclohexanecarboxylate (3.00 g, 15.4 mmol, HCl salt, CAS# 75143-07-6) in DCM (40 mL) was added TEA (1.73 g, 17.0 mmol) and $(Boc)_2O$ (3.72 g, 17.0 mmol) at 0 °C. The mixture was stirred at 25 °C for 16 hours. On completion, the mixture was concentrated *in vacuo*. The crude was purified by silica gel column chromatography to give the title compound(2.30 g, 51% yield) as a colorless oil. ^1H NMR (400MHz, DMSO-d_6) δ 6.74 (d, J = 6.4 Hz, 1H), 3.60 (s, 3H), 2.48 (m, 1H), 1.87 - 1.84 (m, 2H), 1.54 - 1.51 (m, 5H), 1.47 - 1.41 (m, 2H), 1.37 (s, 9H).

[00902] Step 2 - (1s,4s)-Methyl 4-((tert-butoxycarbonyl)(methyl)amino)cyclohexanecarboxylate

[00903] To a solution of methyl 4-(tert-butoxycarbonylamino)cyclohexanecarboxylate (2.00 g, 7.77 mmol) in DMF (20 mL) was added NaH (466 mg, 11.6 mmol, 60% dispersion in mineral oil) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. Then CH_3I (3.31 g, 23.3 mmol) was added and the mixture was stirred at 50 °C for 13.5 hours. On completion, the mixture was diluted with water (120 mL) and extracted with EA (3 X 30 mL), the organic layers were collected, dried over Na_2SO_4, filtered and concentrated to give the title compound (2.10 g, 99%yiled) as a yellow oil. LC-MS (ESI^+) *m/z* 171.9 $(M\text{-}Boc+H)^+$.

[00904] Step 3 - Tert-butyl ((1s,4s)-4-(hydroxymethyl)cyclohexyl)(methyl)carbamate

[00905] To a solution of methyl 4-[tert-butoxycarbonyl(methyl)amino]cyclohexanecarboxylate (1.50 g, 4.75 mmol) in THF (16 mL) and MeOH (4 mL) was added $LiBH_4$ (310 mg, 14.2 mmol) at 0 °C. The mixture was stirred at 60 °C for 14 hours. On completion, the reaction was quenched with water (50 mL) and extracted with EA (3 X 30 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated to give the title compound (1.25 g, 92% yiled) as a yellow oil. LC-MS (ESI^+) *m/z* 144.0 $(M+H\text{-}100)^+$.

[00906] Step 4 - ((1s,4s)-4-((Tert-butoxycarbonyl)(methyl)amino)cyclohexyl)methyl methanesulfonate

[00907] To a solution of tert-butyl N-[4-(hydroxymethyl)cyclohexyl]-N-methyl-carbamate (1.25 g, 3.70 mmol) and TEA (1.12 g, 11.10 mmol) in DCM (15 mL) was added MsCl (847 mg, 7.40 mmol) at 0 °C. The mixture was stirred at 20 °C for 1 hour. On completion, the mixture was diluted with brine (50 mL) and extracted with DCM (2 X 30 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated to give the title compound (1.70 g, 99% yiled) as a yellow oil. LC-MS (ESI^+) *m/z* 221.9 $(M+H-100)^+$.

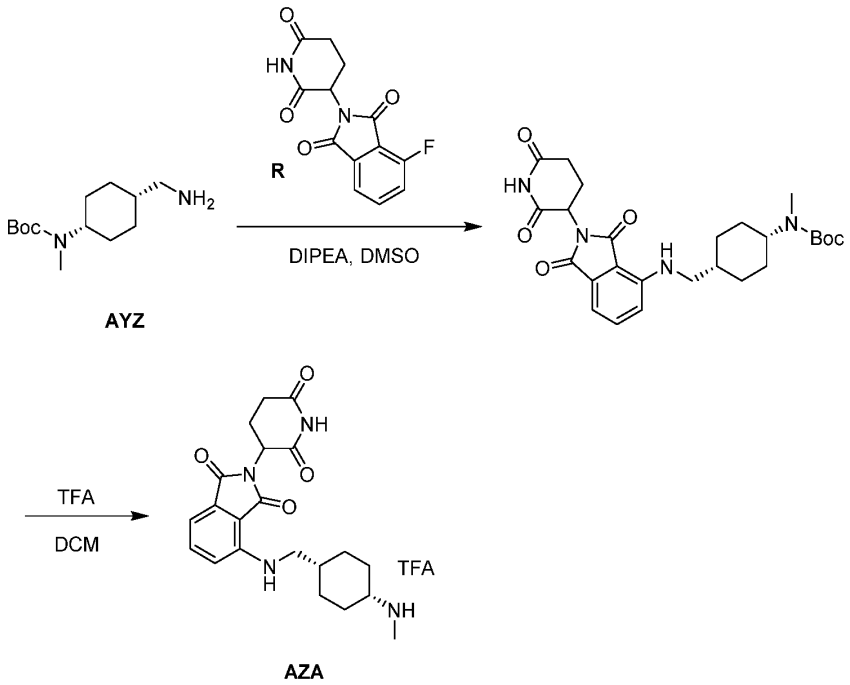
[00908] Step 5 - Tert-butyl ((1s,4s)-4-((1,3-dioxoisoindolin-2-yl)methyl)cyclohexyl)(methyl)carbamate

[00909] To a solution of [4-[tert-butoxycarbonyl(methyl)amino]cyclohexyl]methyl methanesulfonate (1.70 g, 5.29 mmol) in DMF (10 mL) was added (1,3-dioxoisoindolin-2-yl)potassium (1.96 g, 10.5 mmol, CAS# 1074-82-4). The mixture was stirred at 100 °C for 14 hours. On completion, it was extracted with EA (3 X 50 mL) and the organic layers were collected, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by Prep-HPLC(Neu: column: Waters Xbridge C18 150*50mm* 10um; mobile phase: [water(10mM NH4HCO3)-ACN];B%: 38%-68%,11.5min) to give the title product (1.00 g, 50% yield) as a yellow solid. ^1H NMR (400MHz, DMSO-d_6) δ 7.88 - 7.83 (m, 4H), 3.60 - 3.55 (m, 2H), 2.73 - 2.61 (m, 3H), 2.08 (s, 1H), 1.81 - 1.75 (m, 2H), 1.72 - 1.68 (m, 4H), 1.40 - 1.15 (m, 12H); LC-MS (ESI^+) *m/z* 273.2 $(M+H-100)^+$.

[00910] Step 6 - Tert-butyl ((1s,4s)-4-(aminomethyl)cyclohexyl)(methyl)carbamate

[00911] To a solution of tert-butyl N-[4-[(1,3-dioxoisoindolin-2-yl)methyl]cyclohexyl]-N-methyl-carbamate (1.00 g, 2.68 mmol) in EtOH (15 mL) was added $NH_2NH_2.H_2O$ (474 mg, 8.05 mmol). The mixture was stirred at 60 °C for 2 hours. On completion, it was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with PE (30 mL), filtered and the filtrate was concentrated *in vacuo* to give the title compound (600 mg, 92% yield) as a yellow oil. LC-MS (ESI^+) *m/z* 243.3 $(M+H)^+$.

[00912] 2-(2,6-Dioxopiperidin-3-yl)-4-((((1s,4s)-4-(methylamino)cyclohexyl)methyl)amino) isoindoline-1,3-dione (Intermediate AZA)



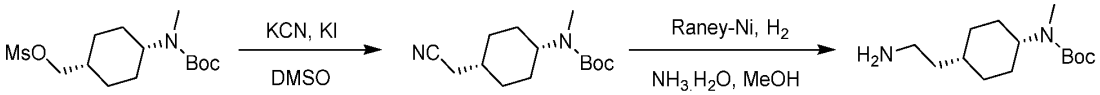
[00913] Step 1 - Tert-butyl ((1s,4s)-4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl) cyclohexyl)(methyl)carbamate

[00914] To a solution of tert-butyl N-[4-(aminomethyl)cyclohexyl]-N-methyl-carbamate (600 mg, 1.46 mmol, Intermediate AYZ) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (605 mg, 2.19 mmol, Intermediate R) in DMSO (10 mL) was added DIPEA (377 mg, 2.92 mmol). The mixture was stirred at 130 °C for 0.5 hour. On completion, the mixture was concentrated *in vacuo*. The residue was purified by reverse-phase-flash (FA condition) to give the title product (450 mg, 61% yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.08 (s, 1H), 7.60 (m, 1H), 7.15 (m, 1H), 7.02 (d, J = 7.2 Hz, 1H), 6.62 (m, 1H), 5.05 (m, 1H), 3.70 (s, 1H), 3.45 (m, 3H), 2.85 (m, 1H), 2.70 - 2.50 (m, 6H), 2.00 (m, 2H), 1.70 - 1.50 (m, 6H), 1.39 - 1.34 (m, 10H). LC-MS (ESI$^+$) *m/z* 399.2 (M+H-100)$^+$.

[00915] Step 2 - 2-(2,6-Dioxopiperidin-3-yl)-4-((((1s,4s)-4-(methylamino)cyclohexyl)methyl)amino) isoindoline-1,3-dione

[00916] A solution of tert-butyl N-[4-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]methyl] cyclohexyl]-N-methyl-carbamate (450 mg, 902 umol) in TFA (1 mL) and DCM (4 mL) was stirred at 20 °C for 2 hours. On completion, the mixture was concentrated *in vacuo* to give the title compound (450 mg, 99% yield) as a yellow oil. LC-MS (ESI$^+$) *m/z* 399.2 (M+H)$^+$.

[00917] Tert-butyl N-[4-(2-aminoethyl)cyclohexyl]-N-methyl-carbamate (Intermediate BGY)



BGY

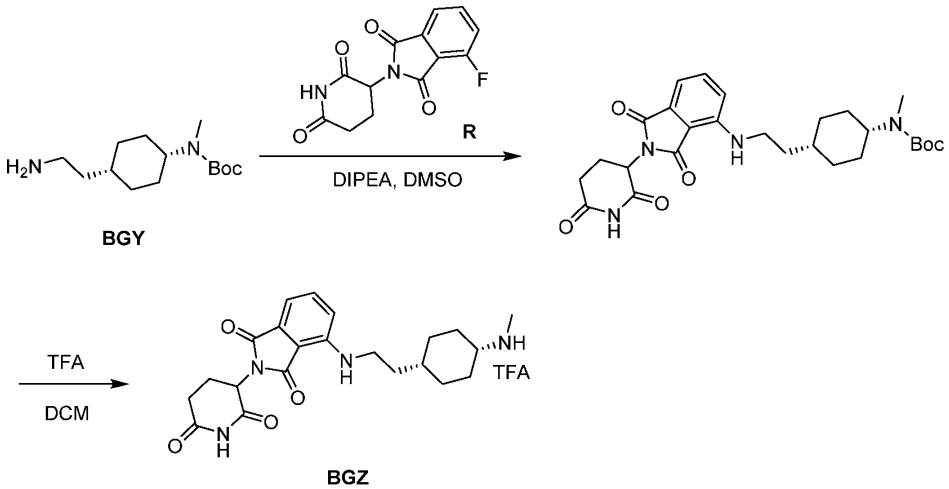
[00918] Step 1 - Tert-butyl N-[4-(cyanomethyl)cyclohexyl]-N-methyl-carbamate

[00919] To a mixture of [4-[tert-butoxycarbonyl(methyl)amino]cyclohexyl]methyl methanesulfonate (4.40 g, 13.6 mmol, synthesized via Steps 1-4 of Intermediate AYZ) in DMSO (45 mL) was added KCN (1.07 g, 16.4 mmol) and KI (3.41 g, 20.5 mmol). The reaction mixture was stirred at 100 °C for 12 hours. On completion, the reaction mixture was diluted with water (120 mL) and extracted with EA (3 X 100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (1.50 g, 43% yield) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 1H), 2.74 (s, 3H), 2.43 (d, J = 8.0 Hz, 2H), 2.24 - 2.13 (m, 1H), 1.87 - 1.77 (m, 2H), 1.77 - 1.67 (m, 2H), 1.62 - 1.48 (m, 4H), 1.46 (s, 9H).

[00920] Step 2 - Tert-butyl N-[4-(2-aminoethyl)cyclohexyl]-N-methyl-carbamate

[00921] To a mixture of tert-butyl N-[4-(cyanomethyl)cyclohexyl]-N-methyl-carbamate (1.30 g, 5.15 mmol) in MeOH (15 mL) and $NH_3{\cdot}H_2O$ (2 mL) was added Raney-Ni (1.30 g, 15.1 mmol). The reaction mixture was stirred at 30 °C for 12 hours under H_2 (50 Psi) atmosphere. On completion, the reaction mixture was filtered and concentrated *in vacuo* to give the title compound (1.30 g, 98% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 - 3.74 (m, 1H), 2.73 (s, 3H), 2.72 - 2.57 (m, 2H), 1.74 (s, 1H), 1.65 - 1.52 (m, 8H), 1.46 (s, 9H), 1.23 - 0.74 (m, 2H).

[00922] 2-(2,6-Dioxo-3-piperidyl)-4-[2-[4(methylamino)cyclohexyl]ethylamino]isoindoline-1,3-dione (Intermediate BGZ)



BGY

BGZ

[00923] Step 1 - Tert-butyl N-[4-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]

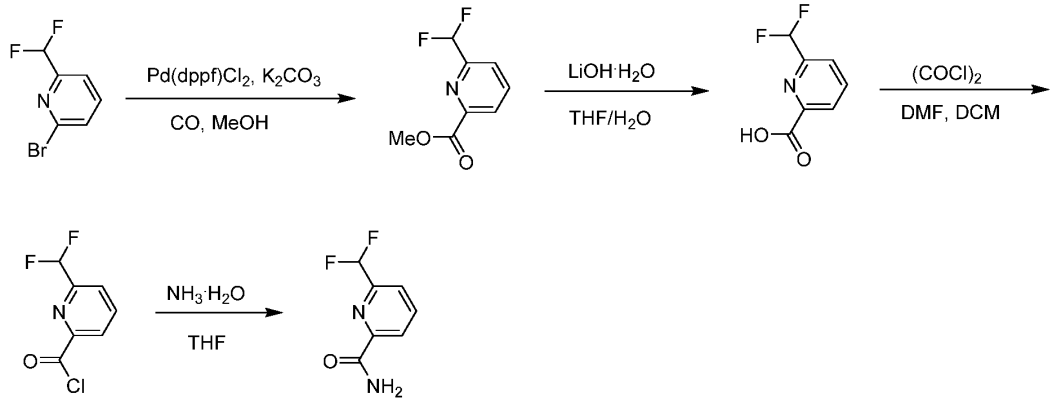
cyclohexyl]-N-methyl-carbamate

[00924] To a mixture of tert-butyl N-[4-(2-aminoethyl)cyclohexyl]-N-methyl-carbamate (1.30 g, 5.07 mmol, Intermediate BGY) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (1.40 g, 5.07 mmol, Intermediate R) in DMSO (15 mL) was added DIPEA (1.97 g, 15.2 mmol). The reaction mixture was stirred at 130 °C for 3 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (1.60 g, 61% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.62 - 7.56 (m, 1H), 7.10 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 6.53 (t, J = 5.6 Hz, 1H), 5.09 - 5.02 (m, 1H), 3.80 - 3.58 (m, 1H), 3.32 (s, 6H), 2.94 - 2.82 (m, 1H), 2.63 - 2.52 (m, 2H), 2.08 - 1.98 (m, 1H), 1.71 - 1.56 (m, 6H), 1.54 - 1.44 (m, 2H), 1.38 (s, 9H), 1.36 - 1.30 (m, 2H); LC-MS (ESI$^+$) *m/z* 513.4 (M+H)$^+$.

[00925] Step 2 - 2-(2,6-Dioxo-3-piperidyl)-4-[2-[4-(methylamino)cyclohexyl]ethylamino]isoindoline-1,3-dione

[00926] To a mixture of tert-butyl N-[4-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl] cyclohexyl]-N-methyl-carbamate (70.0 mg, 136 umol) in DCM (2 mL) was added TFA (2 mL). The reaction mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (62.0 mg, 99% yield) as yellow oil. LC-MS (ESI$^+$) *m/z* 413.3 (M+H)$^+$.

[00927] 6-(Difluoromethyl)pyridine-2-carboxamide (Intermediate AXO)



AXO

[00928] Step 1 - Methyl 6-(difluoromethyl)pyridine-2-carboxylate

[00929] To a solution of 2-bromo-6-(difluoromethyl)pyridine (2.00 g, 9.62 mmol, CAS# 872365-91-8) in MeOH (20 mL) and DMSO (20 mL) was added TEA (2.92 g, 28.8 mmol), $Pd(OAc)_2$ (215 mg, 961 umol) and DPPP (396 mg, 961 umol) at 25 °C. The reaction mixture was stirred at 80 °C for 16 hours under CO (50 Psi). On completion, after cooled to 25 °C, the mixture was diluted with H_2O (60 mL) and extracted

with EA (3 X 20 mL). The combined organic layers were washed by brine (20 mL), dried over by Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (1.60 g, 88% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.0 Hz, 1H), 8.01 (t, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 6.74 (t, J = 54.8 Hz, 1H), 4.01 (s, 3H); LC-MS (ESI^+) m/z 188.1 $(M + H)^+$.

[00930] Step 2 - 6-(Difluoromethyl)pyridine-2-carboxylic acid

[00931] To a solution of methyl 6-(difluoromethyl)pyridine-2-carboxylate (1.40 g, 7.48 mmol) in THF (24 mL) and H_2O (12 mL) was added $LiOH{\cdot}H_2O$ (627 mg, 14.9 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 hours. On completion, the mixture was concentrated *in vacuo*. The residue was purified by reverse phase (0.1% TFA condition) to give the title compound (1.50 g, 98% yield, 85% purity) as a white solid. LC-MS (ESI^+) m/z 174.2 $(M+H)^+$.

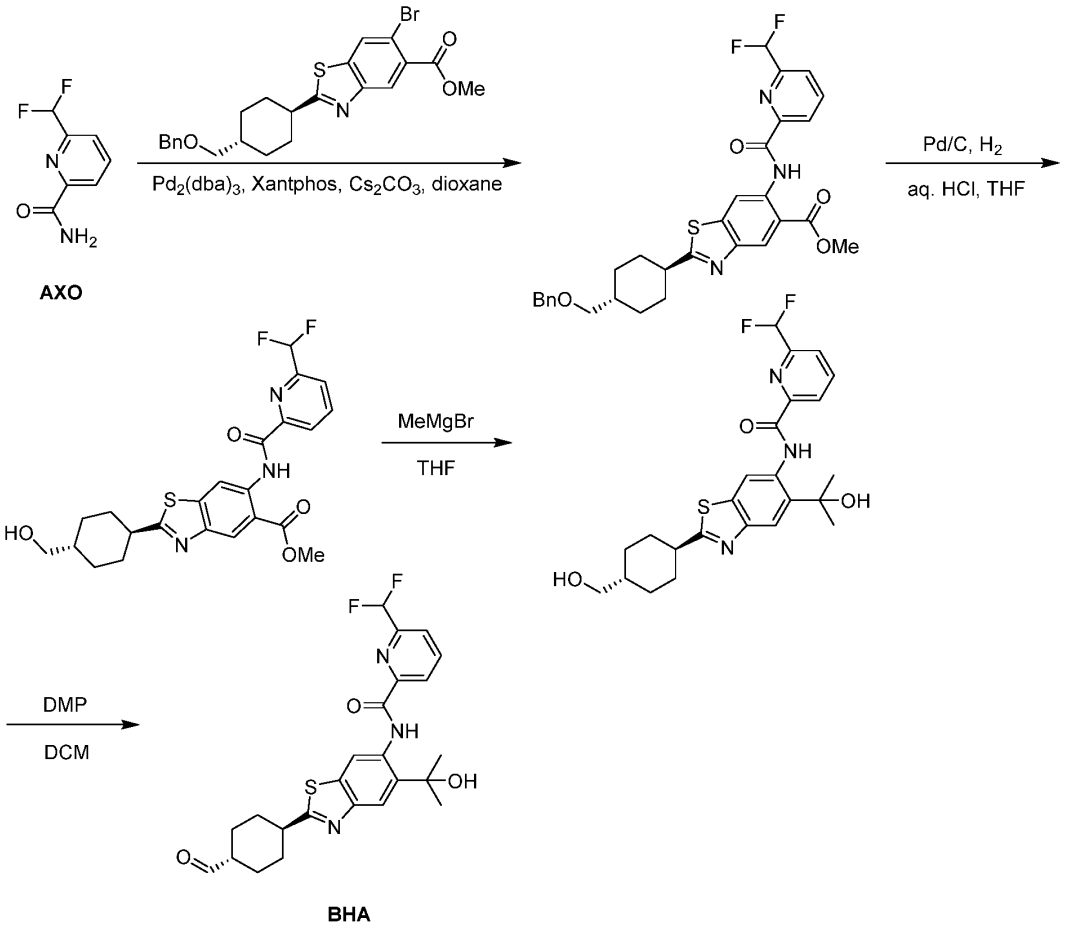
[00932] Step 3 - 6-(Difluoromethyl)pyridine-2-carbonyl chloride

[00933] To a solution of 6-(difluoromethyl)pyridine-2-carboxylic acid (330 mg, 1.81 mmol) in DCM (5 mL) was added $(COCl)_2$ (459 mg, 3.62 mmol) and DMF (13.2 mg, 181 umol) at 0 °C. The mixture was stirred at 0 - 25 °C for 2 hours. On completion, the mixture was concentrated *in vacuo* to give the title compound (340 mg, 98% yield) as yellow oil.

[00934] Step 4 - 6-(Difluoromethyl)pyridine-2-carboxamide

[00935] A solution of 6-(difluoromethyl)pyridine-2-carbonyl chloride (340 mg, 1.77 mmol) in THF (5 mL) was added to $NH_3{\cdot}H_2O$ (4.15 g, 35.5 mmol, 30% solution) at 0°C. The mixture was stirred at 0 - 25 °C for 1 hour. On completion, the reaction mixture was diluted with H_2O (15 mL) and extracted with EA (3 X 5 mL). The combined organic layers were washed by brine (20 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give the title compound (180 mg, 58% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 - 8.15 (m, 2H), 8.05 (s, 1H), 7.92 - 7.87 (m, 1H), 7.80 (s, 1H), 6.99 (t, J = 54.8 Hz, 1H).

[00936] 6-(Difluoromethyl)-N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]pyridine-2-carboxamide (Intermediate BHA)



[00937] Step 1 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[[6-(difluoromethyl)pyridine-2-carbonyl]amino] -1,3-benzothiazole-5-carboxylate

[00938] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate (350 mg, 737.76 umol, synthesized via Steps 1-3 of Intermediate BAW) and 6-(difluoromethyl)pyridine-2-carboxamide (152 mg, 885 umol, Intermediate AXO) in dioxane (10 mL) was added Xantphos (85.3 mg, 147 umol), $Pd_2(dba)_3$ (67.5 mg, 73.7 umol) and Cs_2CO_3 (480 mg, 1.48 mmol) at 25 °C. The reaction mixture was stirred at 80 °C for 12 hrs under N_2. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1 to 8/1) to give the title compound (400 mg, 86% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 - 12.75 (m, 1H), 9.42 (s, 1H), 8.56 - 8.47 (m, 1H), 8.38 - 8.26 (m, 2H), 8.01 (d, J = 7.6 Hz, 1H), 7.39 - 7.27 (m, 5H), 7.23 - 6.94 (m, 1H), 4.49 - 4.42 (m, 2H), 3.99 (s, 3H), 3.31 - 3.29 (m, 2H), 3.14 - 3.00 (m, 1H), 2.21 - 2.13 (m, 1H), 1.94 - 1.86 (m, 2H), 1.73 - 1.51 (m, 3H), 1.50 - 1.36 (m, 1H), 1.25 - 1.06 (m, 2H); LC-MS (ESI$^+$) m/z 566.3 $(M+H)^+$.

[00939] Step 2 - Methyl 6-[[6-(difluoromethyl)pyridine-2-carbonyl]amino]-2-[4-(hydroxymethyl)cyclohexyl]- 1,3-benzothiazole-5-carboxylate

[00940] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[[6-(difluoromethyl)pyridine-2-carbonyl]amino]-1,3-benzothiazole-5-carboxylate (200 mg, 353 umol) in THF (3 mL) was added Pd/C (200 mg, 10 wt %) and HCl (1 M, 353 uL) at 25 °C. The mixture was stirred at 25 °C for 12 hrs under H_2 (15 Psi). On completion, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to give the title compound (160 mg, 95% yield) as yellow oil. LC-MS (ESI^+) m/z 475.9 $(M+H)^+$.

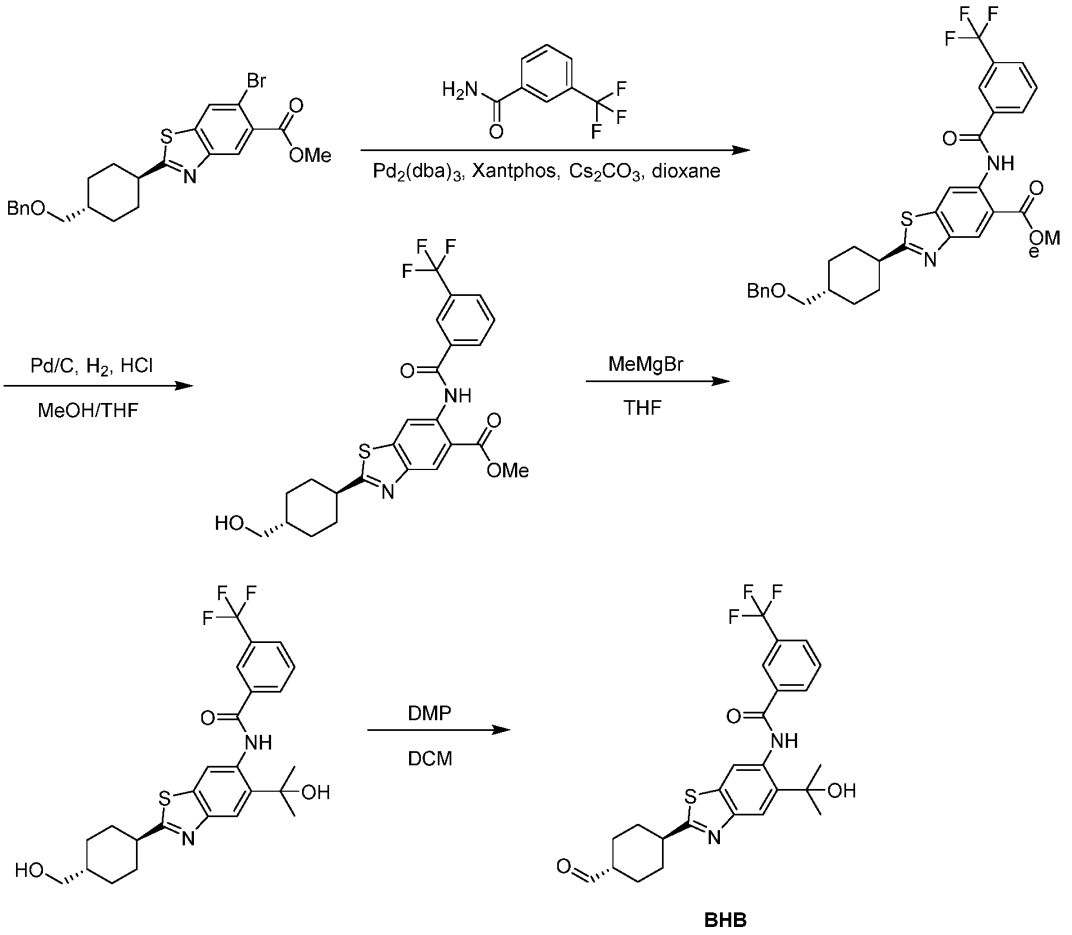
[00941] Step 3 - 6-(Difluoromethyl)-N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)- 1,3-benzothiazol-6-yl]pyridine-2-carboxamide

[00942] To a solution of methyl 6-[[6-(difluoromethyl)pyridine-2-carbonyl]amino]-2-[4-(hydroxymethyl) cyclohexyl]-1,3-benzothiazole-5-carboxylate (160 mg, 336 umol)in THF (2 mL) was added MeMgBr (3 M, 560 uL) at 0 °C. The mixture was stirred at 0 - 25 °C for 3 hrs. On completion, the reaction mixture was quenched by addition sat. aq. NH_4Cl 2 mL at 0 °C and was diluted with H_2O (15 mL) and extracted with EA (3 X 5 mL). The combined organic layers were washed by brine (20 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (50.0 mg, 31% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.79 - 12.60 (m, 1H), 9.14 - 8.99 (m, 1H), 8.37 - 8.27 (m, 2H), 8.00 (d, J = 7.6 Hz, 1H), 7.92 - 7.88 (m, 1H), 7.20 - 6.88 (m, 1H), 6.20 - 6.05 (m, 1H), 3.29 - 3.24 (m, 2H), 3.07 - 2.99 (m, 1H), 2.21 - 2.07 (m, 2H), 1.92 - 1.83 (m, 2H), 1.65 (s, 6H), 1.62 - 1.51 (m, 2H), 1.48 - 1.38 (m, 1H), 1.20 - 1.02 (m, 2H); LC-MS (ESI^+) m/z 476.2 $(M+H)^+$.

[00943] Step 4 - 6-(Difluoromethyl)-N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]pyridine-2-carboxamide

[00944] To a solution of 6-(difluoromethyl)-N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl -ethyl)-1,3-benzothiazol-6-yl]pyridine-2-carboxamide (40.0 mg, 84.1 umol) in DCM (1 mL) was added DMP (46.3 mg, 109 umol) at 25 °C. The reaction mixture was stirred at 25°C for 2 hrs. On completion, the reaction mixture was quenched by addition sat. aq. $Na_2S_2O_3$ (1 mL) and sat. aq. $NaHCO_3$ (1 mL), and then diluted with H_2O 15 mL and were extracted with DCM (3 X 5 mL). The combined organic layers were washed with brine 10 mL (2 X 5 mL), dried over by Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (39.0 mg, 97% yield) as yellow oil. LC-MS (ESI^+) m/z 474.1 $(M+H)^+$.

[00945] N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-3-(trifluoromethyl)benzamide (Intermediate BHB)



BHB

[00946] Step 1 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[[3-(trifluoromethyl)benzoyl]amino]-1,3- benzothiazole-5-carboxylate

[00947] To a mixture of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate (400 mg, 843 umol, synthesized via Steps 1-3 of Intermediate BAW) and 3-(trifluoromethyl)benzamide (159 mg, 843 umol, CAS# 1801-10-1) in dioxane (3 mL) was added $Pd_2(dba)_3$ (77.2 mg, 84.3 umol), Xantphos (97.5 mg, 168 umol) and Cs_2CO_3 (549 mg, 1.69 mmol). The reaction mixture was stirred at 80 °C for 12 hours. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (491 mg, 99% yield) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 9.62 (s, 1H), 9.02 (s, 1H), 8.23 - 8.18 (m, 2H), 8.03 (d, J = 7.6 Hz, 1H), 7.91 (s, 1H), 7.89 - 7.84 (m, 1H), 6.72 (s, 1H), 3.13 - 3.04 (m, 1H), 2.43 - 2.35 (m, 1H), 2.27 - 2.18 (m, 2H), 2.11 - 2.02 (m, 2H), 1.71 - 1.60 (m, 8H), 1.46 - 1.33 (m, 2H).

[00948] Step 2 - Methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-[[3-(trifluoromethyl)benzoyl]amino]-1,3-

benzothiazole-5-carboxylate

[00949] To a mixture of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[[3-(trifluoromethyl)benzoyl]amino]- 1,3-benzothiazole-5-carboxylate (500 mg, 858 umol) and HCl (1 M, 858 uL) in THF (3 mL) and MeOH (3 mL) was added Pd/C (500 mg, 10 wt%). The reaction mixture was stirred at 25 °C for 12 hours under H_2 (15 Psi). On completion, the reaction mixture was filtered and concentrated *in vacuo* to give the title compound (390 mg, 92% yield) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 9.01 (s, 1H), 8.50 - 8.45 (m, 1H), 8.30 - 8.25 (m, 2H), 8.04 (d, J = 8.0 Hz, 1H), 7.93 - 7.84 (m, 1H), 3.91 (s, 3H), 3.27 (d, J = 6.4 Hz, 2H), 3.13 - 3.04 (m, 1H), 2.19 (d, J = 10.4 Hz, 2H), 1.93 - 1.84 (m, 2H), 1.63 - 1.52 (m, 2H), 1.50 - 1.39 (m, 1H), 1.17 - 1.04 (m, 2H); LC-MS (ESI$^+$) *m/z* 493.3 $(M+H)^+$.

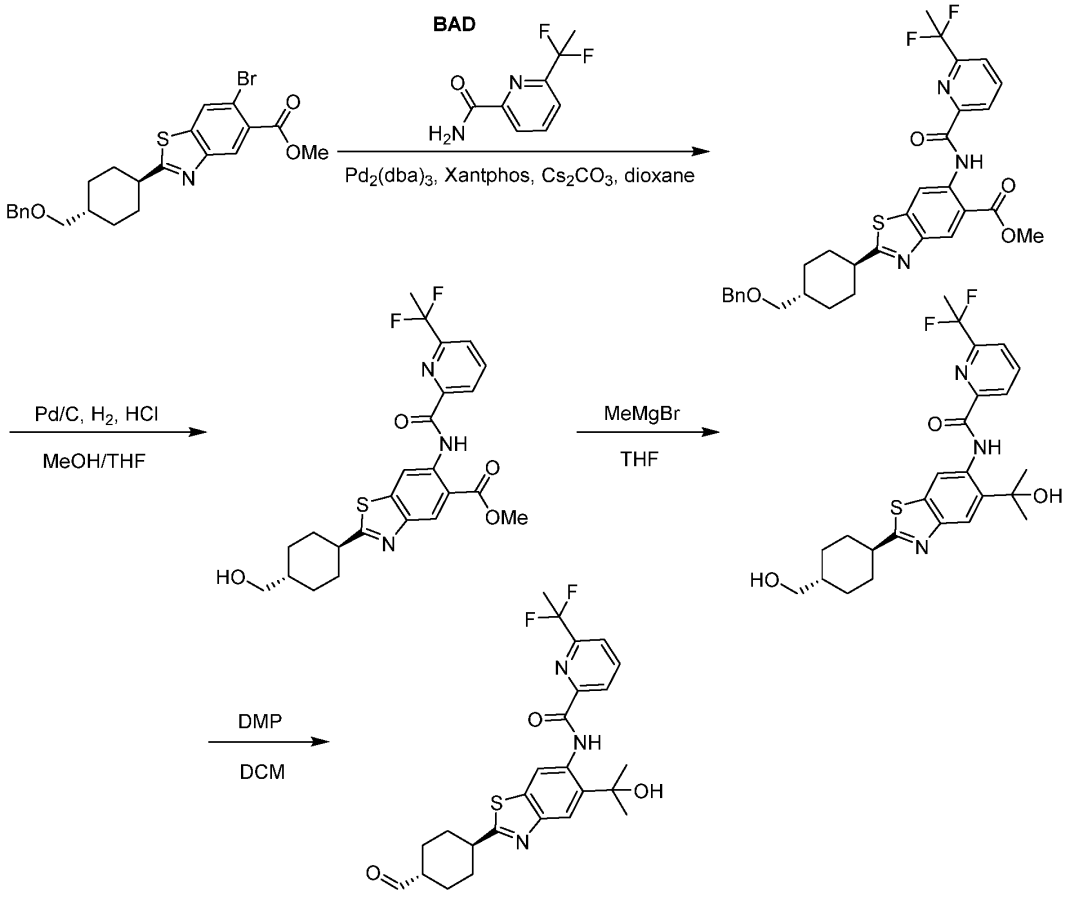
[00950] Step 3 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl] -3-(trifluoromethyl)benzamide

[00951] To a mixture of methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-[[3-(trifluoromethyl)benzoyl]amino] -1,3-benzothiazole-5-carboxylate (340 mg, 690 umol) in THF (4 mL) was added MeMgBr (3 M, 2.30 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 hours. On completion, the reaction mixture was quenched with sat. aq. NH_4Cl (5 mL) and diluted with water (30 mL) and extracted with EA (2 X 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (200 mg, 58% yield) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 9.01 (s, 1H), 8.23 - 8.18 (m, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.89 - 7.83 (m, 1H), 6.73 (s, 1H), 4.45 (s, 1H), 3.27 (d, J = 5.2 Hz, 2H), 3.07 - 2.99 (m, 1H), 2.21 - 2.14 (m, 2H), 1.91 - 1.84 (m, 2H), 1.66 (s, 6H), 1.62 - 1.51 (m, 2H), 1.49 - 1.39 (m, 1H), 1.15 - 1.04 (m, 2H).

[00952] Step 4 - N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-3-(trifluoromethyl)benzamide

[00953] To a mixture of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol -6-yl]-3-(trifluoromethyl)benzamide (200 mg, 406 umol) and $NaHCO_3$ (170 mg, 2.03 mmol) in DCM (5 mL) was added DMP (206 mg, 487 umol). The reaction mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was quenched by sat. aq. $Na_2S_2O_3$ (8 mL) and sat. aq. $NaHCO_3$ (8 mL) at 25 °C, and stirred for 30 minutes. The mixture was extracted with DCM (2 X 20 mL). The organic layer was separated and concentrated *in vacuo* to give the title compound (180 mg, 90% yield) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 9.62 (s, 1H), 9.02 (s, 1H), 8.23 - 8.18 (m, 2H), 8.03 (d, J = 7.6 Hz, 1H), 7.91 (s, 1H), 7.89 - 7.84 (m, 1H), 6.72 (s, 1H), 3.13 - 3.04 (m, 1H), 2.43 - 2.35 (m, 1H), 2.27 - 2.18 (m, 2H), 2.11 - 2.02 (m, 2H), 1.71 - 1.60 (m, 8H), 1.46 - 1.33 (m, 2H); LC-MS (ESI$^+$) *m/z* 491.3 $(M+H)^+$.

[00954] 6-(1,1-Difluoroethyl)-N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]pyridine-2-carboxamide (Intermediate BHC)



BHC

[00955] Step 1 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[[6-(1,1-difluoroethyl)pyridine-2-carbonyl] amino]-1,3-benzothiazole-5-carboxylate

[00956] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate (300 mg, 632 umol, synthesized via Steps 1-3 of Intermediate BAW) in dioxane (7 mL) was added $Pd_2(dba)_3$ (57.9 mg, 63.2 umol), Xantphos (73.1 mg, 126 umol), Cs_2CO_3 (412 mg, 1.26 mmol) and 6-(1,1-difluoroethyl)pyridine-2-carboxamide (129 mg, 695 umol, Intermediate BAD). The mixture was stirred at 80 °C for 16 hrs. On completion, the reaction mixture was filter to give the filtrate and concentrated *in vacuo*. The residue was diluted with DCM (60 mL) and washed with water (2 X 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase (FA condition) to give the title compound (355 mg, 96% yield) as light yellow solid. ^1H NMR (400MHz,

DMSO-d_6) δ 13.01 (s, 1H), 9.46 (s, 1H), 8.51 (s, 1H), 8.37 - 8.22 (m, 2H), 8.02 (d, J = 7.2 Hz, 1H), 7.85 - 7.15 (m, 7H), 4.47 (s, 2H), 3.96 (s, 3H), 3.06 (t, J = 12.4 Hz, 1H), 2.29 (t, J = 19.6 Hz, 3H), 2.17 (d, J = 11.6 Hz, 2H), 1.89 (d, J = 11.2 Hz, 2H), 1.72 - 1.52 (m, 3H), 1.22 - 1.09 (m, 2H).

[00957] Step 2 - Methyl 6-[[6-(1,1-difluoroethyl)pyridine-2-carbonyl]amino]-2-[4-(hydroxymethyl)cyclohexyl] -1,3-benzothiazole-5-carboxylate

[00958] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[[6-(1,1-difluoroethyl)pyridine-2- carbonyl]amino]-1,3-benzothiazole-5-carboxylate (300 mg, 517 umol) in a mixed solvent of MeOH (5 mL) and THF (5 mL) was added HCl (1 M, 103 uL) and Pd/C (150 mg, 10 wt%) under N_2. The suspension was degassed *in vacuo* and purged with H_2 gas 3 times. The mixture was stirred under H_2 (15 psi) at 25°C for 16 hours. On completion, the reaction mixture was filtered and concentrated *in vacuo* to give the title compound (250 mg, 90% yield) as light yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 13.02 (s, 1H), 9.47 (s, 1H), 8.53 (s, 1H), 8.37 - 8.23 (m, 2H), 8.03 (dd, J = 1.2, 7.2 Hz, 1H), 3.97 (s, 3H), 3.27 (d, J = 6.4 Hz, 2H), 3.12 - 3.01 (m, 1H), 2.29 (t, J = 19.2 Hz, 3H), 2.22 - 2.13 (m, 2H), 1.88 (dd, J = 2.4, 13.2 Hz, 2H), 1.66 - 1.51 (m, 2H), 1.47 - 1.45 (m, 1H), 1.18 - 1.02 (m, 2H).

[00959] Step 3 - 6-(1,1-Difluoroethyl)-N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)- 1,3-benzothiazol-6-yl]pyridine-2-carboxamide

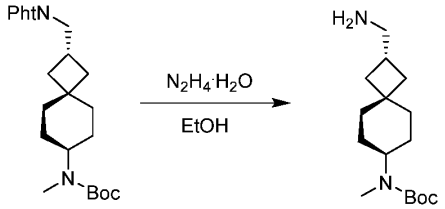
[00960] To a solution of methyl 6-[[6-(1,1-difluoroethyl)pyridine-2-carbonyl]amino]-2-[4-(hydroxymethyl) cyclohexyl]-1,3-benzothiazole-5-carboxylate (50.0 mg, 102 umol) in THF (2 mL) was added MeMgBr (3 M, 170 uL) at 0 °C. The mixture was stirred at 0 °C for 2 hrs. On completion, the reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with EA (3 X 10 ml). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase (FA condition) to give the title compound (45.0 mg, 89% yield) as light yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.61 (s, 1H), 9.13 (s, 1H), 8.36 - 8.26 (m, 2H), 8.01 (dd, J = 1.2, 7.6 Hz, 1H), 7.91 (s, 1H), 6.21 (s, 1H), 4.46 (t, J = 5.2 Hz, 1H), 3.30 - 3.26 (m, 2H), 3.10 - 3.00 (m, 1H), 2.28 - 2.15 (m, 5H), 1.93 - 1.85 (m, 2H), 1.65 (s, 6H), 1.62 - 1.52 (m, 2H), 1.49 - 1.39 (m, 1H), 1.18 - 1.08 (m, 2H); LC-MS (ESI^+) m/z 490.2 $(M+H)^+$.

[00961] Step 4 - 6-(1,1-Difluoroethyl)-N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]pyridine-2-carboxamide

[00962] To a solution of 6-(1,1-difluoroethyl)-N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl- ethyl)-1,3-benzothiazol-6-yl]pyridine-2-carboxamide (30.0 mg, 61.2 umol) in DCM (2 mL) was added DMP (31.1 mg, 73.5 umol). The mixture was stirred at 10 °C for 1 hr. On completion, the reaction was diluted with DCM (10 mL) and then quenched with saturated $Na_2S_2O_3$ (5 mL) and saturated $NaHCO_3$ (5 mL) at 0 °C. The mixture was stirred at 10 °C for 30 minutes. The organic layer was separated and washed with saturated NaCl (10 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the

title compound (26.0 mg, 90% yield) as light yellow solid. LC-MS (ESI^+) *m/z* 488.2 $(M+H)^+$.

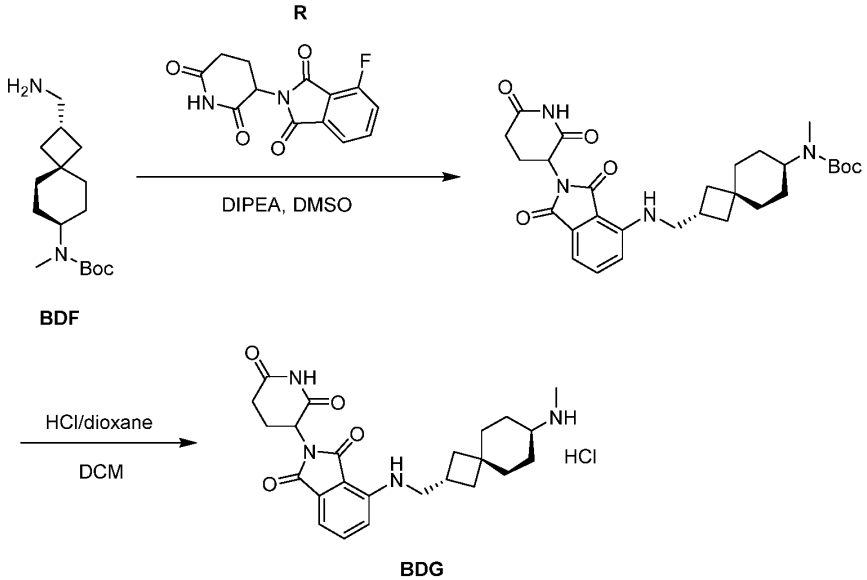
[00963] Tert-butyl N-[2-(aminomethyl)spiro[3.5]nonan-7-yl]-N-methyl-carbamate (Intermediate BDF)



BCP BDF

[00964] To a solution of tert-butyl N-[2-[(1,3-dioxoisoindolin-2-yl)methyl]spiro[3.5]nonan-7-yl]-N-methyl -carbamate (383 mg, 929 umol, Intermediate BCP) in EtOH (6 mL) was added $N_2H_4{\cdot}H_2O$ (232 mg, 4.65 mmol). The reaction mixture was stirred at 80 °C for 2 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was diluted with DCM (40 mL) and filtered. The filtrate was concentrated *in vacuo* to give the title compound (230 mg, 87% yield) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 3.83 - 3.47 (m, 1H), 2.62 (s, 3H), 2.52 - 2.50 (m, 2H), 2.14 (td, J = 7.6, 15.6 Hz, 1H), 1.93 - 1.73 (m, 2H), 1.72 - 1.62 (m, 1H), 1.61 - 1.53 (m, 1H), 1.52 - 1.45 (m, 1H), 1.43 - 1.39 (m, 2H), 1.38 (s, 9H), 1.36 - 1.32 (m, 2H), 1.32 - 1.22 (m, 3H).

[00965] 2-(2,6-Dioxo-3-piperidyl)-4-[[7-(methylamino)spiro[3.5]nonan-2-yl]methylamino] isoindoline-1,3-dione (Intermediate BDG)



BDG

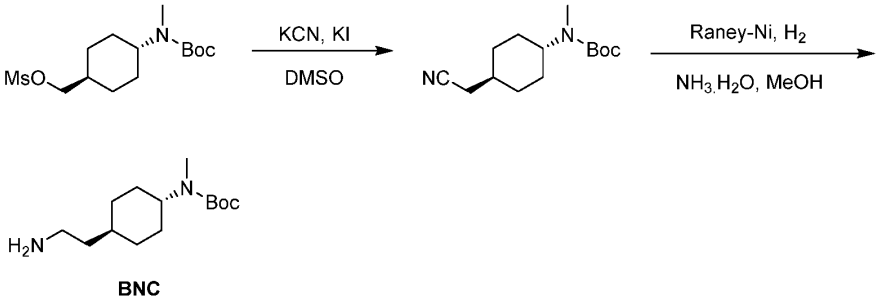
[00966] Step 1 - Tert-butyl N-[2-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4- yl]amino] methyl] spiro[3.5]nonan-7-yl]-N-methyl-carbamate

[00967] To a solution of tert-butyl N-[2-(aminomethyl)spiro[3.5]nonan-7-yl]-N-methyl-carbamate (230 mg, 814 umol, Intermediate BDF) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (224 mg, 814 umol, Intermediate R) in DMSO (3 mL) was added DIPEA (210 mg, 1.63 mmol). The reaction mixture was stirred at 130 °C for 3 hours. On completion, the reaction mixture was diluted with water (15 mL) and extracted with EA (3 X 20 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase (0.1% FA) to give the title compound (280 mg, 63% yield) as yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.49 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 6.19 (t, *J* = 5.2 Hz, 1H), 4.92 (dd, *J* = 5.2, 12.0 Hz, 1H), 4.03 - 3.58 (m, 1H), 3.37 - 3.13 (m, 2H), 2.96 - 2.84 (m, 1H), 2.84 - 2.72 (m, 2H), 2.70 (s, 3H), 2.61 - 2.49 (m, 1H), 2.18 - 2.03 (m, 2H), 1.95 - 1.82 (m, 2H), 1.68 - 1.60 (m, 1H), 1.57 - 1.52 (m, 2H), 1.52 - 1.48 (m, 2H), 1.46 (s, 9H), 1.45 - 1.36 (m, 4H).

[00968] Step 2 - 2-(2,6-Dioxo-3-piperidyl)-4-[[7-(methylamino)spiro[3.5]nonan-2-yl]methylamino] isoindoline-1,3-dione

[00969] To a solution of tert-butyl N-[2-[[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]methyl] spiro[3.5]nonan-7-yl]-N-methyl-carbamate (280 mg, 519 umol) in DCM (4 mL) was added HCl/dioxane (4 M, 4 mL). The reaction mixture was stirred at 20 °C for 0.5 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (240 mg, 97% yield, HCl salt) as yellow solid. LC-MS (ESI^+) *m/z* 439.4 $(M+H)^+$.

[00970] 2-(2,6-Dioxo-3-piperidyl)-4-[methyl-[3-(4-piperidyloxy)propyl]amino]isoindoline-1,3-dione (Intermediate BNC)



BNC

[00971] Step 1 - Tert-butyl N-[4-(cyanomethyl)cyclohexyl]-N-methyl-carbamate

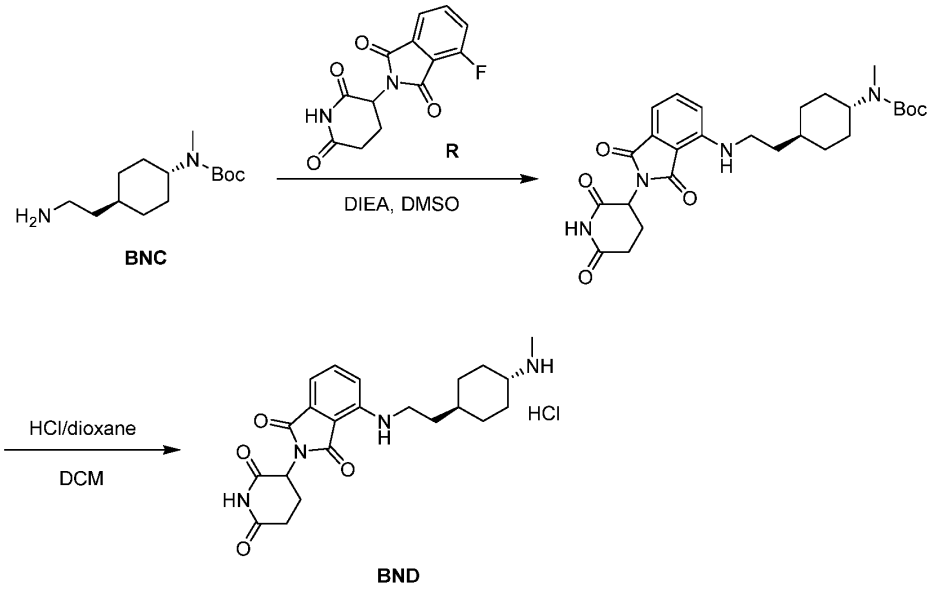
[00972] To a solution of [4-[tert-butoxycarbonyl(methyl)amino]cyclohexyl]methyl methanesulfonate (2.00 g, 6.22 mmol, synthesized via Steps 1-3 of Intermediate AVY) in DMSO (20 mL) was added KCN (486 mg, 7.47 mmol) and KI (1.55 g, 9.33 mmol) and the mixture was stirred at 100 °C for 16 hrs. On completion, the reaction diluted with water (100 mL), then extracted with ethyl acetate (4 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=10/1) to give the title

compound (0.9 g, 57% yield) as white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.21 - 3.46 (m, 1H), 2.84 - 2.59 (m, 3H), 2.26 (d, J = 6.8 Hz, 2H), 2.03 - 1.86 (m, 2H), 1.82 - 1.70 (m, 2H), 1.63 - 1.57 (m, 1H), 1.30 - 1.14 (m, 2H).

[00973] Step 2 - 2-(2,6-Dioxo-3-piperidyl)-4-[methyl-[3-(4-piperidyloxy)propyl]amino]isoindoline-1,3-dione

[00974] To a solution of tert-butyl N-[4-(cyanomethyl)cyclohexyl]-N-methyl-carbamate (650 mg, 2.58 mmol) and $NH_3{\cdot}H_2O$ (1.81 g, 12.8 mmol, 1.98 mL, 25% solution) in MeOH (15 mL) was added Raney-Ni (66.2 mg, 772 umol) under N_2. The suspension was degassed under vacuum and purged with H_2 three times. The mixture was stirred under H_2 (5.19 mg, 2.58 mmol) (50 psi) at 25 °C for 16 hours. On completion, the mixture was filtered and concentrated *in vacuo* to give the title compound (0.66 g, 98% yield) as colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.07 - 3.63 (m, 1H), 2.84 - 2.62 (m, 5H), 1.88 - 1.76 (m, 2H), 1.72 - 1.64 (m, 2H), 1.48 - 1.39 (m, 13H), 1.39 - 1.34 (m, 2H), 1.28 - 1.18 (m, 1H), 1.14 - 0.97 (m, 2H).

[00975] 2-(2,6-Dioxo-3-piperidyl)-4-[2-[4(methylamino)cyclohexyl]ethylamino]isoindoline-1,3-dione (Intermediate BND)



[00976] Step 1 - Tert-butyl N-[4-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]cyclo hexyl]-N-methyl-carbamate

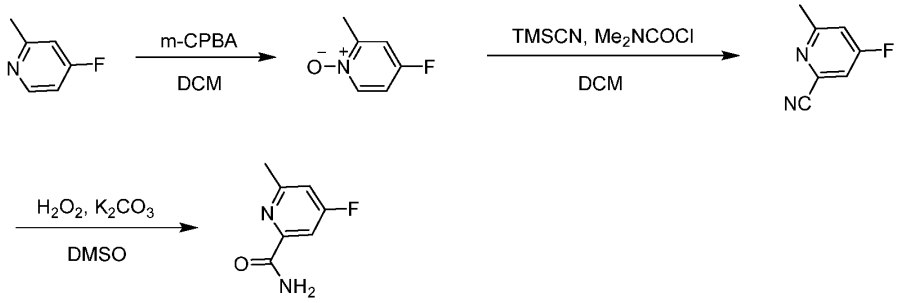
[00977] To a solution of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (170 mg, 615 umol, Intermediate R) in DMSO (2 mL) was added tert-butyl N-[4-(2-aminoethyl)cyclohexyl]-N-methyl-carbamate (173 mg, 677 umol, Intermediate BNC) and DIEA (238 mg, 1.85 mmol) and the mixture was stirred at 130 °C for 6 hrs. On completion, the reaction mixture was diluted with water (20 mL), and then

extracted with EA (3 X 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (FA condition) to give the title compound (0.20 g, 63% yield) as yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.08 (d, *J* = 1.0 Hz, 1H), 7.55 - 7.45 (m, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 6.18 (t, *J* = 5.2 Hz, 1H), 4.96 - 4.86 (m, 1H), 4.08 - 3.61 (m, 1H), 3.35 - 3.19 (m, 2H), 2.95 - 2.74 (m, 3H), 2.74 - 2.68 (m, 3H), 2.19 - 2.11 (m, 1H), 1.86 (d, *J* = 12.0 Hz, 2H), 1.71 (d, *J* = 10.0 Hz, 2H), 1.61 - 1.55 (m, 2H), 1.51 - 1.42 (m, 11H), 1.38 - 1.30 (m, 1H), 1.20 - 1.00 (m, 2H).

[00978] Step 2 - 2-(2,6-Dioxo-3-piperidyl)-4-[2-[4-(methylamino)cyclohexyl]ethylamino]isoindoline-1,3-dione

[00979] To a solution of tert-butyl N-[4-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl] cyclohexyl]-N-methyl-carbamate (70 mg, 136 umol) in DCM (1 mL) was added HCl/dioxane (4 M, 682 uL) and the mixture was stirred at 25°C for 1 hr. On completion, the reaction was concentrated *in vacuo* to give the title compound (60.0 mg, 95% yield, HCl) as yellow solid. LC-MS (ESI^+) *m/z* 413.1 $(M+H)^+$.

[00980] 4-Fluoro-6-methyl-pyridine-2-carboxamide (Intermediate BNE)



BNE

[00981] Step 1 - 4-fluoro-2-methyl-1-oxido-pyridin-1-ium

[00982] To a solution of 4-fluoro-2-methyl-pyridine (5.00 g, 38.2 mmol, CAS# 766-16-5) in DCM (200 mL) was added m-CPBA (12.3 g, 57.3 mmol) at 25 °C. The mixture was stirred at 25 °C for 2 hours. On completion, the reaction was quenched with sat. aq. Na_2SO_3 (20 mL). The mixture was diluted with water (40 mL), and extracted with DCM (4 X 100 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (4.80 g, 95% yield) as light brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (dd, *J* = 5.6, 7.2 Hz, 1H), 7.51 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.28 (*J* = 3.6, 7.2 Hz, 1H), 2.34 (s, 3H).

[00983] Step 2 - 4-Fluoro-6-methyl-pyridine-2-carbonitrile

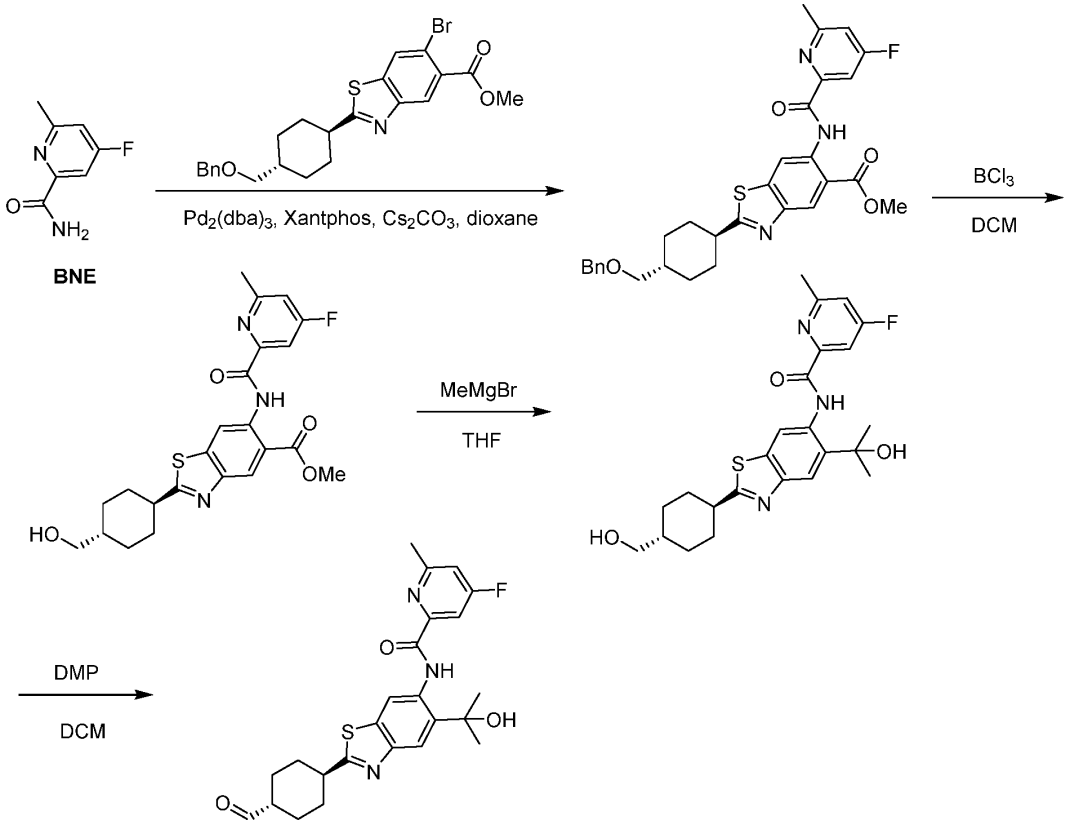
[00984] To a solution of 4-fluoro-2-methyl-1-oxido-pyridin-1-ium (2.5 g, 19.6 mmol) in DCM (100 mL) was added TMSCN (3.90 g, 39.3 mmol, CAS# 7677-24-9) and $(CH_3)_2NCOCl$ (2.75 g, 25.6 mmol,

CAS# 79-44-7) and the mixture was stirred at 25 °C for 12 hours. On completion, the mixture was concentrated *in vacuo*. The residue was diluted with water (30 mL), and extracted with EA (3 X 80 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE: EA = 15: 1 - 5: 1) to give the title compound (1.67 g, 62% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (dd, J = 2.4, 8.6 Hz, 1H), 7.61 (dd, J = 2.4, 9.6 Hz, 1H), 3.08 (s, 1H), 2.98 (s, 1H), 2.54 (s, 3H).

[00985] Step 3- 4-Fluoro-6-methyl-pyridine-2-carboxamide

[00986] To a solution of 4-fluoro-6-methyl-pyridine-2-carbonitrile (0.8 g, 5.88 mmol) in DMSO (12 mL) was added K_2CO_3 (812 mg, 5.88 mmol,) at 25 °C, and then the mixture was added H_2O_2 (1.33 g, 11.7 mmol, 30% solution) slowly. The mixture was then stirred at 25 °C for 16 hours. On completion, the reaction was quenched with sat. aq. Na_2SO_3 (5.0 mL). The mixture was then filtered and the cake was washed with EA (30 mL). The filtrate and washing were combined and diluted with water (20 mL), and extracted with EA (3 X 45 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE: EA = 50: 1 - 20: 1) to give the title compound as white solid (734 mg, 80% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.76 (s, 1H), 7.61 (dd, J = 2.4, 9.6 Hz, 1H), 7.39 (dd, J = 2.0, 9.6 Hz, 1H), 2.55 (s, 3H); LC-MS (ESI$^+$) m/z 155.2 $(M+H)^+$.

[00987] 4-Fluoro-N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-methyl-pyridine-2-carboxamide (Intermediate BNF)



BNF

[00988] Step 1 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[(4-fluoro-6-methyl-pyridine-2-carbonyl) amino]-1,3-benzothiazole-5-carboxylate

[00989] A mixture of 4-fluoro-6-methyl-pyridine-2-carboxamide (117 mg, 758 umol, Intermediate BNE), methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate (300 mg, 632 umol, synthesized via Steps 1-3 of Intermediate BAW), Xantphos (73.2 mg, 126 umol), Cs_2CO_3 (412 mg, 1.26 mmol) and $Pd_2(dba)_3$ (57.9 mg, 63.2 umol) in dioxane (12 mL) was stirred at 80 °C for 16 hours under N_2. On completion, after cooled to 25 °C, the mixture was filtered and the cake was washed with DCM (80 mL). The filtrate and washing were combined and concentrated *in vacuo*. The residue was diluted with water (30 mL), and extracted with DCM (3 X 90 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE: EA = 50: 1 - 10: 1) to give the title compound as white solid (305 mg, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 9.39 (s, 1H), 8.48 (s, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.54 - 7.48 (m, 1H), 7.40 - 7.24 (m, 5H), 4.47 (s, 2H), 3.98 (s, 3H), 3.31 - 3.28 (m, 2H), 3.10 - 3.01 (m, 1H), 2.64 (s, 3H), 2.55 (s, 1H), 2.21 - 2.12 (m, 2H), 1.93 - 1.85 (m, 2H), 1.59 - 1.55 (m, 2H), 1.20 -

1.10 (m, 2H).

[00990] Step 2 - Methyl 6-[(4-fluoro-6-methyl-pyridine-2-carbonyl)amino]-2-[4-(hydroxymethyl)cyclohexyl]- 1,3-benzothiazole-5-carboxylate

[00991] To a solution of methyl 2-[4-(benzyloxymethyl) cyclohexyl]-6-[(4-fluoro-6-methyl-pyridine-2- carbonyl)amino]-1,3-benzothiazole-5-carboxylate (255 mg, 465 umol) in DCM (30 mL) was added BCl_3 (1 M, 4.66 mL) at 0 °C. Then the mixture was stirred at 25 °C for 2 hours. On completion, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL). The mixture was diluted with water (10 mL), and extracted with EA (3 X 35 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE: EA = 20: 1 - 5: 1) to give the title compound as white solid (190 mg, 90 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 9.40 (s, 1H), 8.49 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.53 (dd, J = 2.0, 9.6 Hz, 1H), 4.46 (t, J = 5.2 Hz, 1H), 3.99 (s, 3H), 3.27 (t, J = 6.0 Hz, 2H), 3.11 - 2.98 (m, 1H), 2.65 (s, 3H), 2.18 (d, J = 10.4 Hz, 2H), 1.92 - 1.83 (m, 2H), 1.58 - 1.54 (m, 2H), 1.45 - 1.43 (m, 1H), 1.12 - 1.09 (m, 2H); LC-MS (ESI$^+$) m/z 458.2 $(M+H)^+$.

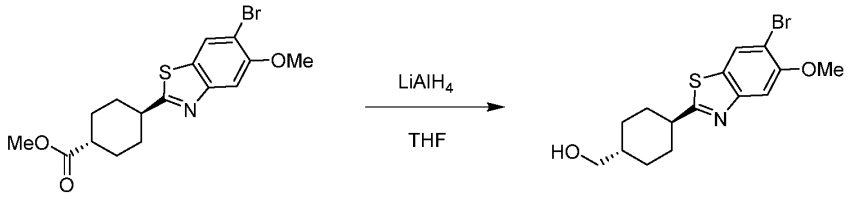
[00992] Step 3 - 4-Fluoro-N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3 -benzothiazol -6-yl]-6-methyl-pyridine-2-carboxamide

[00993] To a solution of methyl 6-[(4-fluoro-6-methyl-pyridine-2-carbonyl) amino]-2-[4-(hydroxymethyl) cyclohexyl]-1,3-benzothiazole-5-carboxylate (120 mg, 262 umol) in THF (15 mL) was added MeMgBr (3 M, 874 uL) and the mixture was stirred at 25 °C for 2 hours. On completion, the reaction was quenched with NH_4Cl (1.0 mL) and the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE: EA = 10: 1 - 3: 1) to give the title compound (115 mg, 95% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 9.05 (d, J = 2.4 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 9.6 Hz, 1H), 7.49 (d, J = 10.0 Hz, 1H), 6.10 (s, 1H), 3.28 (s, 2H), 3.06 - 3.00 (m, 1H), 2.63 (s, 3H), 2.17 (d, J = 12.8 Hz, 2H), 1.88 (d, J = 11.2 Hz, 2H), 1.64 (s, 6H), 1.59 - 1.50 (m, 2H), 1.44 (dd, J = 2.0, 8.6 Hz, 2H), 1.10 (d, J = 11.2 Hz, 2H).

[00994] Step 4 - 4-Fluoro-N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6- methyl-pyridine-2-carboxamide

[00995] To a solution of 4-fluoro-N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3- benzothiazol-6-yl]-6-methyl-pyridine-2-carboxamide (80.0 mg, 174 umol) in THF (6 mL) was added DMP (111 mg, 262 umol) at 0 °C. Then the mixture was stirred at 25 °C for 1.5 hours. On completion, the reaction was quenched with sat. aq. Na_2SO_3 (5.0 mL). The mixture was diluted with water (10 mL), and extracted with EA (3 X 45 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (80.0 mg, 99% yield) as white solid. LC-MS (ESI+) m/z 456.3 $(M+H)^+$.

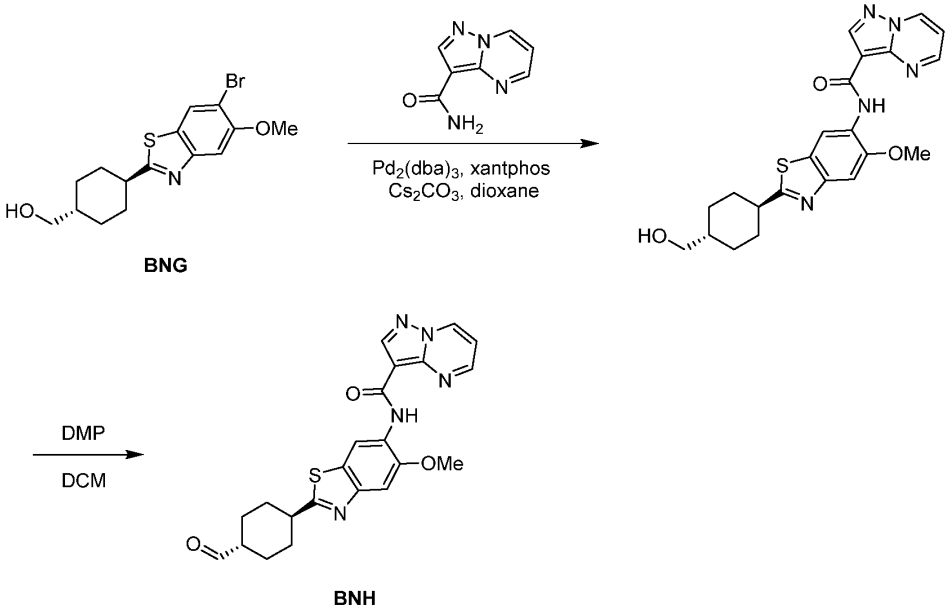
[00996] ((1R,4R)-4-(6-Bromo-5-methoxybenzo[d]thiazol-2-yl)cyclohexyl)methanol (Intermediate BNG)



BFN BNG

[00997] To a solution of methyl 4-(6-bromo-5-methoxy-1,3-benzothiazol-2-yl)cyclohexanecarboxylate (200 mg, 520 umol, Intermediate BFN) in the THF (4 mL) was added $LiAlH_4$ (39.5 mg, 1.04 mmol) at -40 °C and the mixture was stirred at -40 °C for 1 hr. On completion, the mixture was quenched with water (0.1 mL) and NaOH (15% aq., 0.1 mL). Then the mixture was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=5/1 to 1/1) to give the title compound (170 mg, 92% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.50 (s, 1H), 3.97 (s, 3H), 3.55 (d, *J* = 6.4 Hz, 2H), 3.03 (tt, J = 3.6, 12.4 Hz, 1H), 2.35 - 2.25 (m, 2H), 2.04 - 1.96 (m, 2H), 1.75 - 1.65 (m, 2H), 1.65 - 1.60 (m, 1H), 1.24 - 1.14 (m, 2H).

[00998] N-(2-((1R,4R)-4-formylcyclohexyl)-5-methoxybenzo[d]thiazol-6-yl)pyrazolo[1,5-a]pyrimidine -3-carboxamide (Intermediate BNH)



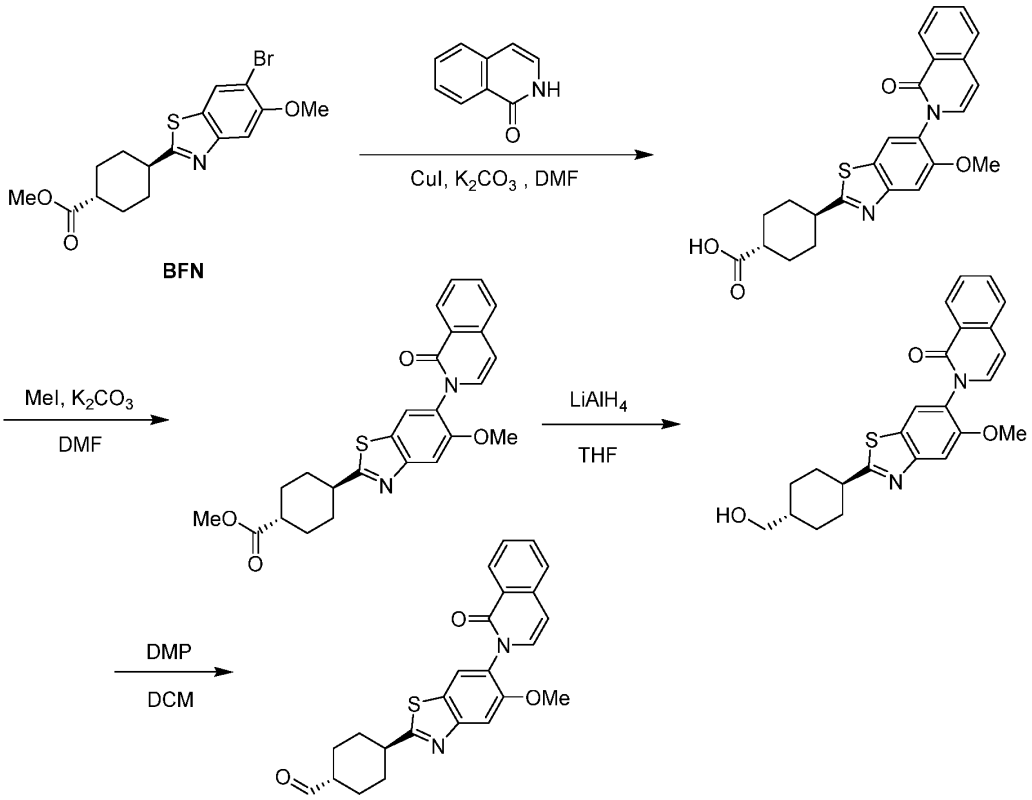
[00999] Step 1 - N-(2-((1r,4r)-4-(hydroxymethyl)cyclohexyl)-5-methoxybenzo[d]thiazol-6-yl)pyrazolo[1,5-a] pyrimidine-3-carboxamide

[001000] To a solution of [4-(6-bromo-5-methoxy-1,3-benzothiazol-2-yl)cyclohexyl]methanol (170 mg, 477 umol, Intermediate BNG) and pyrazolo[1,5-a]pyrimidine-3-carboxamide (77.4 mg, 477 umol, CAS# 774549-55-2) in the dioxane (3 mL) was added $Pd_2(dba)_3$ (43.7 mg, 47.7 umol), Xantphos (55.2 mg, 95.4 umol) and Cs_2CO_3 (310 mg, 954 umol). The mixture was stirred at 100 °C for 12 hrs under N_2. On completion, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate=5/1 to DCM: MeOH = 20:1) to give the title compound (100 mg, 43% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.50 (s, 1H), 9.15 (s, 1H), 8.77 (d, J = 4.0 Hz, 1H), 8.65 - 8.61 (m, 1H), 8.40 (s, 1H), 7.54 (s, 1H), 7.07 (dd, *J* = 4.8, 6.8 Hz, 1H), 3.58 - 3.52 (m, 2H), 3.19 (s, 3H), 3.09 - 3.01 (m, 1H), 2.37 - 2.26 (m, 2H), 2.04 - 1.96 (m, 2H), 1.77 - 1.63 (m, 3H), 1.38 - 1.31 (m, 1H), 1.25 - 1.13 (m, 2H).

[001001] Step 2 - N-(2-((1r,4r)-4-formylcyclohexyl)-5-methoxybenzo[d]thiazol-6-yl)pyrazolo[1,5-a]pyrimidine -3-carboxamide

[001002] To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-methoxy-1,3-benzothiazol-6-yl]pyrazolo [1,5-a]pyrimidine-3-carboxamide (80 mg, 183 umol) in the DCM (2 mL) was added DMP (93.1 mg, 219 umol, 67.9 uL). The mixture was stirred at 25 °C for 1 hr. On completion, the mixture was quenched by saturated $Na_2S_2O_3$ (aq. 1 mL) and $NaHCO_3$ (aq. 1 mL). The mixture was extracted with DCM (10 mL), then the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate=0/1 to DCM: MeOH = 20:1) to give the title compound (20.0 mg, 24% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 9.71 (s, 1H), 9.16 (s, 1H), 8.84 (dd, *J* = 1.7, 7.0 Hz, 1H), 8.79 (s, 1H), 8.77 (dd, *J* = 1.6, 4.4 Hz, 1H), 7.53 (s, 1H), 7.07 (dd, *J* = 4.4, 7.0 Hz, 1H), 4.07 (s, 3H), 3.09 - 3.06 (m, 1H), 2.43 - 2.32 (m, 3H), 2.25 - 2.21 (m, 2H), 1.82 - 1.70 (m, 2H), 1.56 - 1.44 (m, 2H).

[001003] (1R,4R)-4-(5-Methoxy-6-(1-oxoisoquinolin-2(1H)-yl)benzo[d]thiazol-2-yl) cyclohexanecarbaldehyde (Intermediate BNI)



[001004] Step 1 - (1R,4R)-4-(5-Methoxy-6-(1-oxoisoquinolin-2(1H)-yl)benzo[d]thiazol-2-yl)cyclohexane carboxylic acid

[001005] To a solution of methyl 4-(6-bromo-5-methoxy-1,3-benzothiazol-2-yl)cyclohexanecarboxylate (500 mg, 1.30 mmol, Intermediate BFN) and 2H-isoquinolin-1-one (189 mg, 1.30 mmol) in the DMF (5 mL) was added CuI (124 mg, 651 umol) and K_2CO_3 (360 mg, 2.60 mmol). The mixture was stirred at 130 °C for 36 hrs under N_2. On completion, the mixture was diluted with EA (100 mL) and washed with water (3 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (400 mg, 71% yield) as a yellow solid. LC-MS (ESI^+) m/z 435.0 $(M+1)^+$.

[001006] Step 2 - (1R,4R)-Methyl 4-(5-methoxy-6-(1-oxoisoquinolin-2(1H)-yl)benzo[d]thiazol-2-yl) cyclohexanecarboxylate

[001007] To a solution of 4-[5-methoxy-6-(1-oxo-2-isoquinolyl)-1,3-benzothiazol-2-yl]cyclohexanecarboxylic acid (100 mg, 230 umol) in the DMF (2 mL) was added K_2CO_3 (63.6 mg, 460 umol) and MeI (163 mg, 1.15 mmol). The mixture was stirred at 25 °C for 12 hrs. On completion, the

mixture was diluted with EA (20 mL) and washed with water (3 x 20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate=10/1 to 5/1) to give the title compound (80.0 mg, 78% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.0 Hz, 1H), 7.81 - 7.77 (m, 1H), 7.71 - 7.66 (m, 1H), 7.64 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.54 - 7.49 (m, 1H), 7.08 - 7.03 (m, 1H), 6.56 (d, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.27 - 3.19 (m, 1H), 3.10 (tt, *J* = 3.2, 11.6 Hz, 1H), 2.46 - 2.38 (m, 1H), 2.38 - 2.30 (m, 1H), 2.23 - 2.13 (m, 2H), 1.83 - 1.58 (m, 4H).

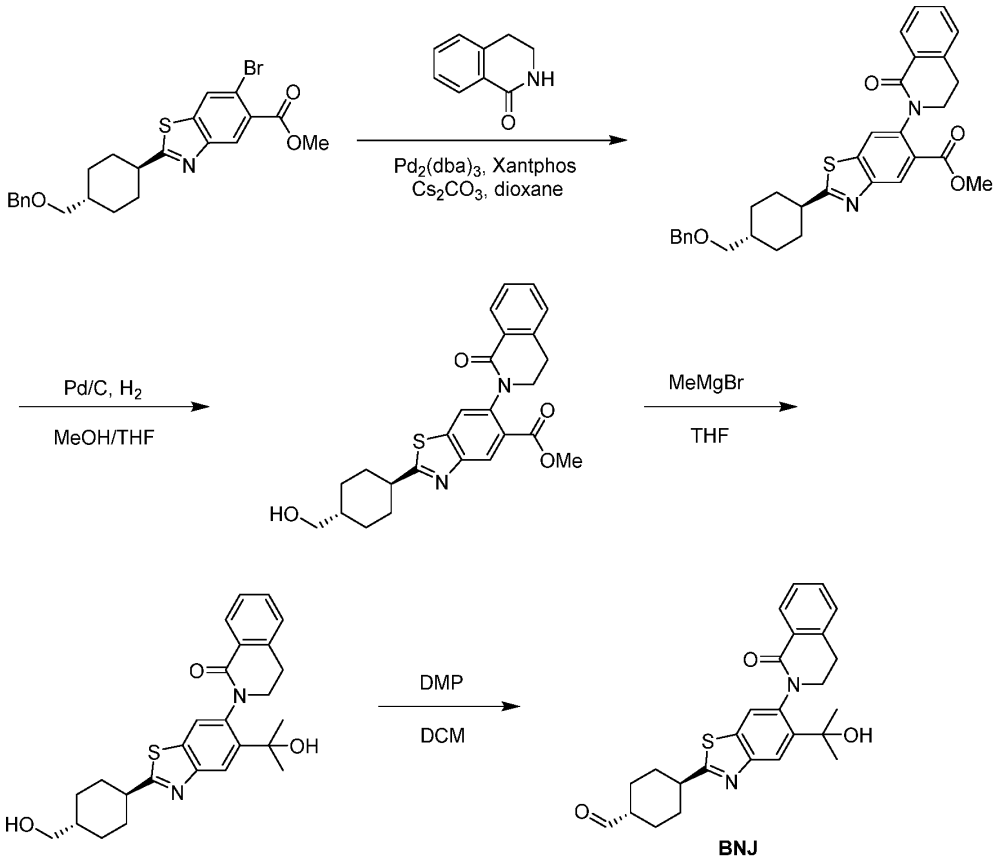
[001008] Step 3 - 2-(2-((1R,4R)-4-(Hydroxymethyl)cyclohexyl)-5-methoxybenzo[d]thiazol-6-yl)isoquinolin-1 (2H)-one

[001009] To a solution of methyl 4-[5-methoxy-6-(1-oxo-2-isoquinolyl)-1,3-benzothiazol-2-yl] cyclohexanecarboxylate (5.00 mg, 111 umol) in the THF (2 mL) was added $LiAlH_4$ (8.46 mg, 223 umol) at -40 °C. Then the mixture was stirred at 0 °C for 1 hr. On completion, the reaction mixture was quenched with water (0.1 mL) and NaOH (15% aq, 0.1 mL). Then the mixture was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by prep-TLC (ethyl acetate) to give the title compound (40.0 mg, 85% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.72 - 7.66 (m, 1H), 7.65 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 3.54 (d, *J* = 6.4 Hz, 2H), 3.07 (tt, *J* = 3.6, 12.0 Hz, 1H), 2.35 - 2.27 (m, 2H), 2.00 (dd, *J* = 2.4, 13.6 Hz, 2H), 1.76 - 1.64 (m, 2H), 1.64 - 1.56 (m, 1H), 1.24 - 1.14 (m, 2H).

[001010] Step 4 - (1R,4R)-4-(5-Methoxy-6-(1-oxoisoquinolin-2(1H)-yl)benzo[d]thiazol-2-yl) cyclohexanecarbaldehyde

[001011] To a solution of 2-[2-[4-(hydroxymethyl)cyclohexyl]-5-methoxy-1,3-benzothiazol-6-yl] isoquinolin-1-one (75.0 mg, 178 umol) in the DCM (1 mL) was added DMP (90.8 mg, 214 umol) and the mixture was stirred at 25 °C for 1 hr. On completion, the mixture was quenched with saturated $Na_2S_2O_3$ (aq. 1 mL) and $NaHCO_3$ (aq. 1 mL). Then the mixture was extracted with DCM (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (70.0 mg, 94% yield) as a white solid. LC-MS (ESI^+) m/z 419.0 $(M+1)^+$.

[001012] (1R,4R)-4-(5-(2-hydroxypropan-2-yl)-6-(1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)benzo [d]thiazol-2-yl)cyclohexanecarbaldehyde (Intermediate BNJ)



[001013] Step 1 - Methyl 2-((1R,4R)-4-((benzyloxy)methyl)cyclohexyl)-6-(1-oxo-3,4-dihydroisoquinolin -2(1H)-yl)benzo[d]thiazole-5-carboxylate

[001014] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate (500 mg, 1.05 mmol, synthesized via Steps 1-3 of Intermediate BAW) and 3,4-dihydro-2H-isoquinolin-1-one (162 mg, 1.11 mmol, CAS# 1196-38-9) in dioxane (5 mL) was added $Pd_2(dba)_3$ (96.5 mg, 105 umol), Cs_2CO_3 (686 mg, 2.11 mmol) and Xantphos (121 mg, 210 umol). The mixture was stirred at 80 °C for 12 hours. On completion, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=100/1 to 20/1) to give the title compound (360 mg, 58% yield) as a brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.03 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.73 (s, 1H), 7.42 - 7.37 (m, 1H), 7.27 (s, 2H), 7.24 - 7.16 (m, 5H), 4.45 (s, 2H), 4.03 - 3.94 (m, 1H), 3.92 - 3.80 (m, 1H), 3.74 (s, 3H), 3.28 (d, J = 6.4 Hz, 3H), 3.10 (d, *J* = 2.4, 6.8 Hz, 1H), 3.06 - 2.93 (m, 1H), 2.26 - 2.16 (m, 2H), 2.00 - 1.90 (m, 2H), 1.75 - 1.66 (m, 1H), 1.65 - 1.53 (m, 2H), 1.16 - 1.05 (m, 2H); LC-MS (ESI^+) m/z 541.2 $(M+H)^+$.

[001015] Step 2 - Methyl 2-((1R,4R)-4-(hydroxymethyl)cyclohexyl)-6-(1-oxo-3,4-

dihydroisoquinolin-2(1H)-yl) benzo[d]thiazole-5-carboxylate

[001016] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-(1-oxo-3,4-dihydroisoquinolin-2-yl) -1,3-benzothiazole-5-carboxylate (330 mg, 610 umol) in MeOH (3 mL) and THF (3 mL) was added Pd/C (50.0 mg, 10 wt%). The mixture was then stirred at 25 °C for 12 hours under hydrogen atmosphere (50 psi). On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 100/1 to 20/1) to give the title compound (180 mg, 65% yield) as an off-white solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.13 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.83 (s, 1H), 7.52 - 7.44 (m, 1H), 7.41 - 7.35 (m, 1H), 7.29 - 7.25 (m, 1H), 4.14 - 4.03 (m, 1H), 4.01 - 3.89 (m, 1H), 3.83 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.42 - 3.30 (m, 1H), 3.24 - 3.16 (m, 1H), 3.14 - 3.03 (m, 1H), 2.37 - 2.28 (m, 2H), 2.07 - 1.97 (m, 2H), 1.77 - 1.59 (m, 2H), 1.36 (t, *J* = 5.6 Hz, 1H), 1.28 - 1.14 (m, 2H); LC-MS (ESI+) m/z 451.2 $(M+H)^+$.

[001017] Step 3 - 2-(2-((1R,4R)-4-(hydroxymethyl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl) -3,4-dihydroisoquinolin-1(2H)-one

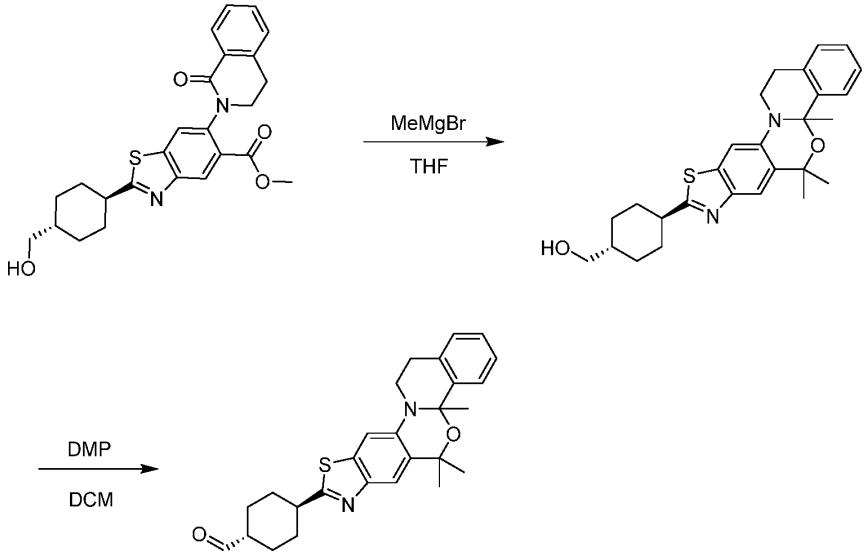
[001018] To a solution of methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-(1-oxo-3,4-dihydroisoquinolin-2-yl)-1,3- benzothiazole-5-carboxylate (50.0 mg, 110 umol) in THF (1 mL) was added MeMgBr (3 M, 184 uL, 554 umol) at 0 °C and the mixture was stirred at 0 °C for 1 hour. On completion, the reaction mixture was quenched by addition sat. NH_4Cl (20 mL) at 0 °C, and then diluted with H_2O (30 mL) and extracted with DCM (3 X 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10: 1) to give the title compound (30.0 mg, 48% yield) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.15 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.66 (s, 1H), 7.53 - 7.46 (m, 1H), 7.42 - 7.36 (m, 1H), 7.27 (s, 1H), 4.08 (dt, *J* = 4.4, 12.0 Hz, 1H), 3.94 - 3.85 (m, 1H), 3.54 (d, *J* = 6.0 Hz, 2H), 3.51 - 3.40 (m, 1H), 3.12 - 2.99 (m, 2H), 2.28 (dd, *J* = 2.8, 10.0 Hz, 2H), 1.99 (d, *J* = 10.8 Hz, 2H), 1.75 (s, 3H), 1.72 (s, 3H), 1.70 (br d, *J* = 3.2 Hz, 1H), 1.67 (*d*, *J* = 3.2 Hz, 1H), 1.65 - 1.62 (m, 1H), 1.23 - 1.12 (m, 2H); LC-MS (ESI^+) m/z 451.3 $(M+H)^+$.

[001019] Step 4 - (1R,4R)-4-(5-(2-hydroxypropan-2-yl)-6-(1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)benzo [d]thiazol-2-yl)cyclohexanecarbaldehyde

[001020] To a solution of 2-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol- 6-yl]-3,4-dihydroisoquinolin-1-one (30.0 mg, 66.5 umol) in DCM (1 mL) was added DMP (42.3 mg, 99.8 umol) and the mixture was stirred at 25 °C for 0.5 hour. On completion, the reaction mixture was quenched by addition sat. $NaHSO_3$ (20 mL) and sat. $NaHCO_3$ (20 mL) at 0 °C, and then diluted with H_2O (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound

(29.0 mg, 99% yield) as an off-white solid. LC-MS (ESI^+) m/z 449.3 $(M+H)^+$.

[001021] (1R,4R)-4-(4b,6,6-trimethyl-4b,6,13,14-tetrahydrothiazolo[4",5":4',5']benzo[1',2':4,5][1,3]oxazino[2,3-a]isoquinolin-9-yl)cyclohexanecarbaldehyde (Intermediate BNK)



BNK

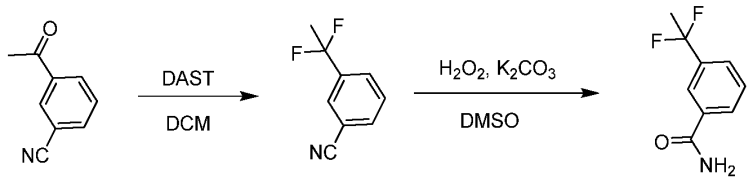
[001022] Step 1 - ((1R,4R)-4-(4b,6,6-trimethyl-4b,6,13,14-tetrahydrothiazolo[4",5":4',5']benzo[1',2':4,5][1,3]oxazino[2,3-a]isoquinolin-9-yl)cyclohexyl)methanol

[001023] To a solution of methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-(1-oxo-3,4-dihydroisoquinolin-2-yl)-1,3- benzothiazole-5-carboxylate (370 mg, 821 umol, synthesized via Steps 1-2 of Intermediate BNJ) in THF (10 mL) was added MeMgBr (3 M, 2.74 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. On completion, the reaction mixture was quenched by addition sat. aq. NH_4Cl (50 mL) at 0 °C, and then diluted with H_2O (50 mL) and extracted with DCM (3 X 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 100: 1 to 20: 1) to give the title compound (140 mg, 37% yield) as a brown solid. ^1H NMR (400 MHz, chloroform-*d*) δ 7.78 (s, 1H), 7.60 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.38 (s, 1H), 7.31 - 7.19 (m, 2H), 7.16 - 7.09 (m, 1H), 3.84 (d, *J* = 12.0 Hz, 1H), 3.54 (d, *J* = 6.0 Hz, 2H), 3.36 (s, 1H), 3.17 - 2.94 (m, 3H), 2.31 - 2.28 (m, 2H), 2.01 - 1.99 (m, 2H), 1.80 (s, 3H), 1.76 - 1.56 (m, 4H), 1.44 (s, 3H), 1.20 - 1.18 (m, 2H); LC-MS (ESI^+) m/z 449.2 $(M+H)^+$.

[001024] Step 2 - (1R,4R)-4-(4b,6,6-trimethyl-4b,6,13,14-tetrahydrothiazolo[4",5":4',5']benzo[1',2':4,5][1,3] oxazino[2,3-a]isoquinolin-9-yl)cyclohexanecarbaldehyde

[001025] To a solution of [4-(25,25,26-trimethyl-30-oxa-31-thia-27,28-diazapentacyclohenicosa-3(5),4(6), 7(18),8(20),16,19(21),22(27)-heptaen-22-yl)cyclohexyl]methanol (140 mg, 312 umol) in DCM (5 mL) was added DMP (172 mg, 405 umol) at 0 °C. Then the mixture was stirred at 25 °C for 0.5 hour. On completion, the reaction mixture was quenched by addition sat. aq. $NaHSO_3$ (50 mL) and sat. aq. $NaHCO_3$ (50 mL) at 0 °C. Then the mixture was diluted with H_2O (50 mL) and extracted with DCM (3 X 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 20:1) to give the title compound (51.0 mg, 34% yield) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.78 (s, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.38 (s, 1H), 7.31 - 7.26 (m, 1H), 7.25 - 7.20 (m, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 3.91 - 3.80 (m, 1H), 3.43 - 3.31 (m, 1H), 3.19 - 2.93 (m, 3H), 2.38 - 2.36 (m, 3H), 2.22 - 2.20 (m, 2H), 1.81 (s, 3H), 1.78 - 1.69 (m, 2H), 1.57 (s, 1H), 1.51 (s, 3H), 1.48 (m,1H), 1.44 (s, 3H). LC-MS (ESI^+) m/z 447.2 $(M+H)^+$.

[001026] 3-(1,1-Difluoroethyl)benzamide (Intermediate BNL)



BNL

[001027] Step 1 - 3-(1,1-Difluoroethyl)benzonitrile

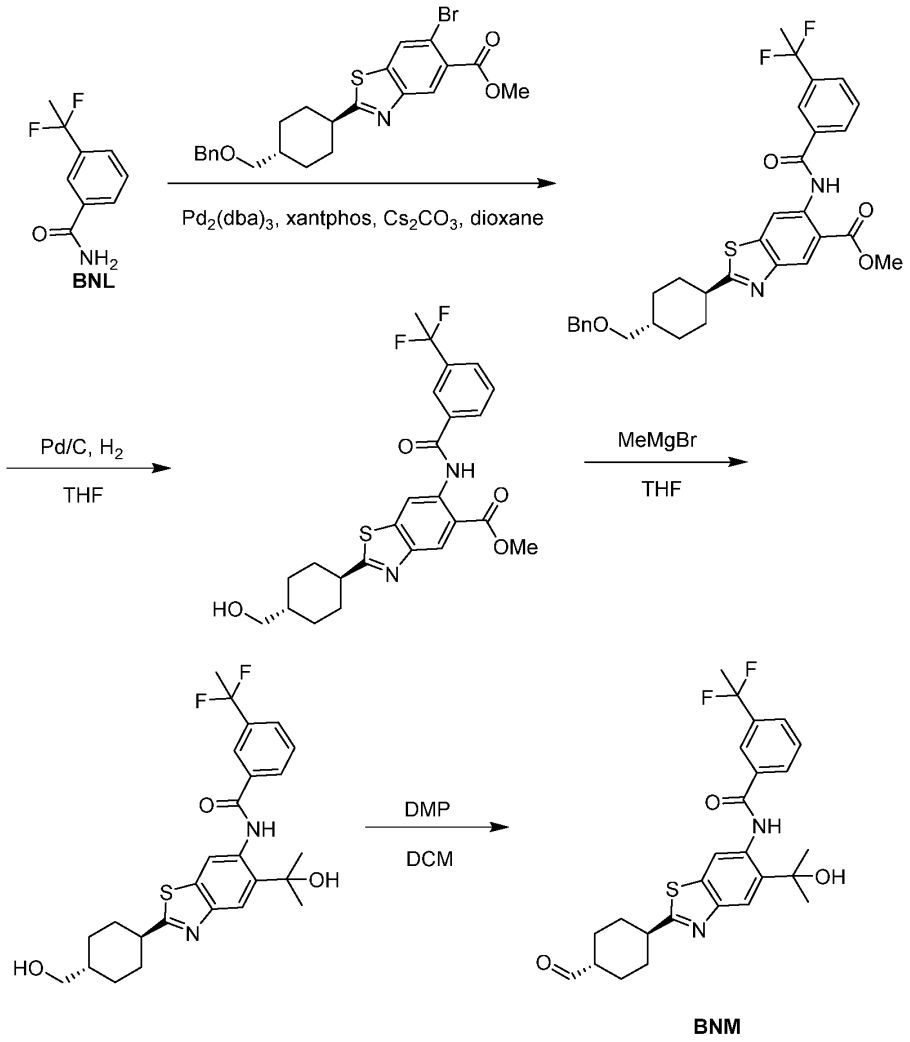
[001028] To a solution of 3-acetylbenzonitrile (2.00 g, 13.78 mmol, CAS# 6136-68-1) in DCM (40 mL) was added DAST (15.5 g, 96.4 mmol) and the mixture was stirred at 35 °C for 16 hours. On completion, the reaction mixture was poured into ice/10% aq. K_2CO_3 (300 mL) slowly. Then the mixture was partitioned and the aqueous phase was extracted with ethyl acetate (3 x 120 mL). The combine organic layer was washed with brine (40 mL), filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE: EA = 50:1-10:1) to give the title compound (1.48 g, 64% yield) as light yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.92 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.78 - 7.64 (m, 1H), 2.00 (t, *J* = 19.2 Hz, 3H); LC-MS (ESI^+) m/z 167.2 $(M+H)^+$.

[001029] Step 2 - 3-(1,1-Difluoroethyl)benzamide

[001030] To a mixture of 3-(1,1-difluoroethyl)benzonitrile (1.38 g, 8.26 mmol) K_2CO_3 (1.14 g, 8.26 mmol) in DMSO (18 mL) was added H_2O_2 (1.87 g, 16.5 mmol, 30% solution) slowly at 25 °C. Then the mixture was stirred at 25 °C for 16 hours. On completion, the reaction was quenched with sat. aq. Na_2SO_3 (15 mL). The mixture was then diluted with water (20 mL), and extracted with ethyl acetate (3 x 60 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated

in vacuo to give the title compound (1.50 g, 98% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 8.05 (s, 1H), 8.02 - 7.97 (m, 1H), 7.72 - 7.70 (m, 1H), 7.61 - 7.55 (m, 1H), 7.50 (s, 1H), 2.99 (s, 2H), 2.54 (s, 4H), 1.99 (t, J = 18.8 Hz, 3H).

[001031] 3-(1,1-Difluoroethyl)-N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]benzamide (Intermediate BNM)



[001032] Step 1 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[[3-(1,1-difluoroethyl)benzoyl]amino]-1,3- benzothiazole-5-carboxylate

[001033] To a solution of 3-(1,1-difluoroethyl)benzamide (70.2 mg, 379 umol, Intermediate BNL), methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate (150 mg, 316 umol, synthesized via Steps 1-3 of Intermediate BAW) in dioxane (3.5 mL) was added $Pd_2(dba)_3$ (28.9 mg, 31.6

umol), Xantphos (36.6 mg, 63.24 umol), Cs_2CO_3 (103 mg, 316 umol) at 25 °C. Then the mixture was stirred at 80 °C for 16 hours under N_2. On completion, after cooled to 25°C, the mixture was filtered and the cake was washed with EA (30 mL). The filtrate and washing were combined and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (PE: EA = 20:1-5:1) to give the title compound (170 mg, 93 % yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 9.09 (s, 1H), 8.49 (s, 1H), 8.15 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.90 - 7.83 (m, 1H), 7.79 - 7.68 (m, 1H), 7.39 - 7.28 (m, 5H), 4.48 (s, 2H), 3.93 (s, 3H), 3.30 (s, 2H), 3.10 (J = 3.6, 11.9 Hz, 1H), 2.19 (d, J = 10.4 Hz, 2H), 2.05 (t, J = 19.2 Hz, 3H), 1.91 (dd, J = 2.4, 13.2 Hz, 2H), 1.70 - 1.68 (m, 1H), 1.65 - 1.55 (m, 2H), 1.21 - 1.15 (m, 2H).

[001034] Step 2 - Methyl 6-[[3-(1,1-difluoroethyl)benzoyl]amino]-2-[4-(hydroxymethyl)cyclohexyl]-1,3- benzothiazole-5-carboxylate

[001035] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[[3-(1,1-difluoroethyl)benzoyl]amino]- 1,3-benzothiazole-5-carboxylate (200 mg, 345 umol) in THF (4 mL) was added HCl (2 M, 345 uL) and Pd/C (200 mg, 10 wt%) at 25 °C. The mixture was stirred at 25 °C for 16 hours under H_2 (15 psi). On completion, the mixture was filtered and the cake was washed with EA (60 mL). The filtrate and washing were combined and concentrated *in vacuo*. The mixture was diluted with water (20 mL), then extracted with EA (3 X 20 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (150 mg, 89 % yield) as light yellow solid. LC-MS (ESI$^+$) m/z 489.2 $(M+H)^+$.

[001036] Step 3 - 3-(1,1-Difluoroethyl)-N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)- 1,3-benzothiazol-6-yl]benzamide

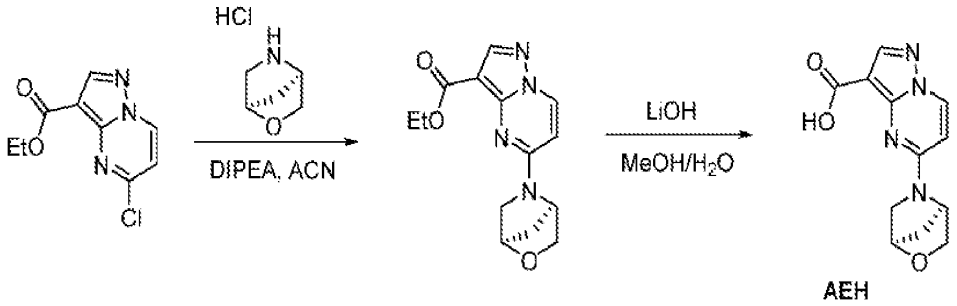
[001037] To a solution of methyl 6-[[3-(1,1-difluoroethyl)benzoyl]amino]-2-[4-(hydroxymethyl)cyclohexyl]- 1,3-benzothiazole-5-carboxylate (200 mg, 409 umol) in THF (12 mL) was added MeMgBr (3 M, 1.36 mL) at 0 °C. Then the mixture was stirred at 25 °C for 2 hours. On completion, the reaction was quenched with sat. aq. NH_4Cl (5 mL). The mixture was diluted with water (50 mL), and extracted with EA (3 X 25 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (PE: EA = 20:1-1:1) to give the title compound (150 mg, 75 % yield) as light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 9.12 (s, 1H), 8.19 (s, 1H), 8.05 (d, J = 7.2 Hz, 1H), 7.94 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.63 - 7.54 (m, 1H), 7.38 - 7.35 (m, 2H), 4.54 (s, 1H), 3.55 (d, J = 6.0 Hz, 2H), 2.44 - 2.37 (m, 1H), 2.33 - 2.31 (m, 3H), 2.05 (s, 1H), 2.04 (s, 1H), 1.99 (s, 2H), 1.95 (s, 1H), 1.82 (s, 6H), 1.73 - 1.71 (m, 1H), 1.69 (d, J = 3.6 Hz, 1H), 1.20 (dd, J = 2.8, 13.6 Hz, 2H); LC-MS (ESI$^+$) m/z 489.2 $(M+H)^+$.

[001038] Step 4 - 3-(1,1-Difluoroethyl)-N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-

1,3- benzothiazol-6-yl]benzamide

[001039] To a solution of 3-(1,1-difluoroethyl)-N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl- ethyl)-1,3-benzothiazol-6-yl]benzamide (35.0 mg, 71.6 umol) in DCM (2 mL) was added DMP (45.5 mg, 107 umol) at 25 °C. The mixture was stirred at 25 °C for 2 hours. On completion, the reaction was quenched with sat. aq. $Na_2S_2O_3$ (1 mL) and sat. aq. $NaHCO_3$ (3 mL). The mixture was diluted with water (10 mL), then extracted with DCM (3 X 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (30.0 mg, 86% yield) as light yellow solid. LC-MS (ESI$^+$) m/z 487.2 $(M+H)^+$.

[001040] 5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Intermediate AEH)



[001041] Step 1 - Ethyl 5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine -3-carboxylate

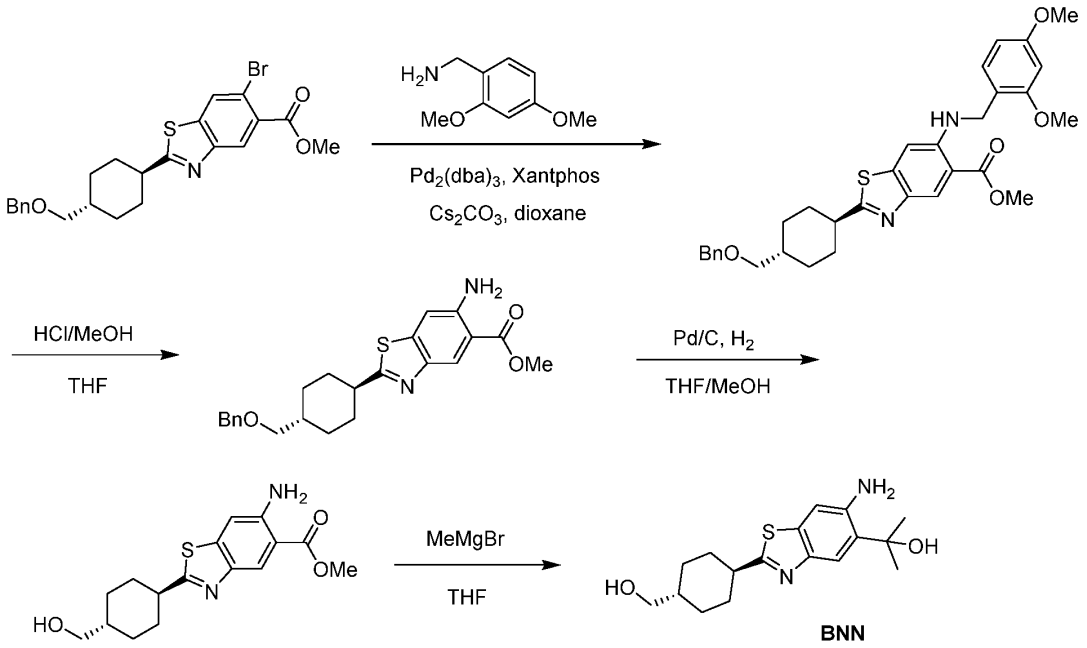
[001042] To a solution of ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (200 mg, 886 umol, CAS# 1224944-77-7) and (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane (144 mg, 1.06 mmol, HCl salt, CAS# 661470-56-0) in ACN (5.00 mL) was added DIPEA (343 mg, 2.66 mmol). The mixture was stirred at 60 °C for 3 hours. On completion, the reaction mixture was concentrated *in vacuo*, then diluted with water (5 mL) and extracted with EA (2 X 10 mL). The combined organic layers were washed with brine (2 X 30 mL), dried over Na_2SO_4, concentrated *in vacuo* to give the title compound (180 mg, 70 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 - 8.18 (m, 2H), 6.12 (s, 1H), 5.46 (s, 1H), 4.77 (s, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.06 - 3.87 (m, 2H), 3.75 - 3.38 (m, 2H), 2.09 - 1.90 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H).

[001043] Step 2 - 5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

[001044] To a solution of ethyl 5-[(1R, 4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3- carboxylate (150 mg, 520 umol) in MeOH (10.0 mL) and H_2O (2.00 mL) was added LiOH H_2O (43.6 mg, 1.04 mmol). The mixture was stirred at 60 °C for 16 hours. On completion, the reaction mixture was quenched with water (1 mL), and concentrated *in vacuo* to remove MeOH. Then the mixture was acidified with HCl (1 N) until the pH = 5. The aqueous phase was extracted with EA (3 X 5 mL). The

combined organic layer was washed with brine (2 X 10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (135 mg, 99 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 - 9.30 (m, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.28 (s, 1H), 6.44 - 6.12 (m, 1H), 5.29 - 4.58 (m, 2H), 4.00 - 3.85 (m, 2H), 3.77 - 3.49 (m, 2H), 2.20 - 1.97 (m, 2H).

[001045] 2-[6-Amino-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazol-5-yl]propan-2-ol (Intermediate BNN)



[001046] Step 1 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[(2,4-dimethoxyphenyl)methylamino]-1,3- benzothiazole-5-carboxylate

[001047] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate (3.00 g, 6.32 mmol, synthesized via Steps 1-3 of Intermediate BAW) in dioxane (20 mL) was added $Pd_2(dba)_3$ (579 mg, 632 umol), Xantphos (731 mg, 1.26 mmol), Cs_2CO_3 (4.12 g, 12.6 mmol) and (2,4-dimethoxyphenyl) methanamine (1.27 g, 7.59 mmol). The mixture was stirred at 80 °C for 3 hours. On completion, the mixture was concentrated *in vacuo* to give the residue. The residue was purified by column chromatography (SiO_2, PE: EA = 5:1 to 0:1) to give the title compound (3.2 g, 92% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.97 (t, *J* = 5.6 Hz, 1H), 7.30 - 7.20 (m, 4H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.92 (s, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 6.35 (dd, *J* = 2.4, 8.4 Hz, 1H), 4.44 (s, 2H), 4.31 (d, *J* = 5.6 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.71 (s, 3H), 3.26 (d, *J* = 6.4 Hz, 2H), 2.87 (tt, *J* = 3.6, 12.0 Hz, 1H), 2.19 - 2.10 (m, 2H), 1.95 - 1.88 (m, 2H), 1.72 - 1.61 (m, 1H), 1.60 - 1.47 (m, 3H), 1.15 - 1.02 (m, 2H).

[001048] Step 2 - Methyl 6-amino-2-[4-(benzyloxymethyl)cyclohexyl]-1,3-benzothiazole-5-

carboxylate

[001049] To a mixture of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-[(2,4-dimethoxyphenyl)methylamino]- 1,3-benzothiazole-5-carboxylate (3.60 g, 6.42 mol) in THF (30 mL) was added HCl/MeOH (4 M, 3.21 mL). The mixture was stirred at 20 °C for 0.5 hour. On completion, the mixture was concentrated *in vacuo* to give the title compound (1.90 g, 72% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.41 - 7.29 (m, 5H), 7.07 (s, 1H), 5.75 (s, 2H), 4.54 (s, 2H), 3.93 (s, 3H), 3.36 (d, *J* = 6.4 Hz, 2H), 2.98 (tt, *J* = 3.6, 12.0 Hz, 1H), 2.31 - 2.20 (m, 2H), 2.08 - 1.98 (m, 2H), 1.84 - 1.74 (m, 1H), 1.73 - 1.55 (m, 3H), 1.24 – 1.14 (m, 2H).

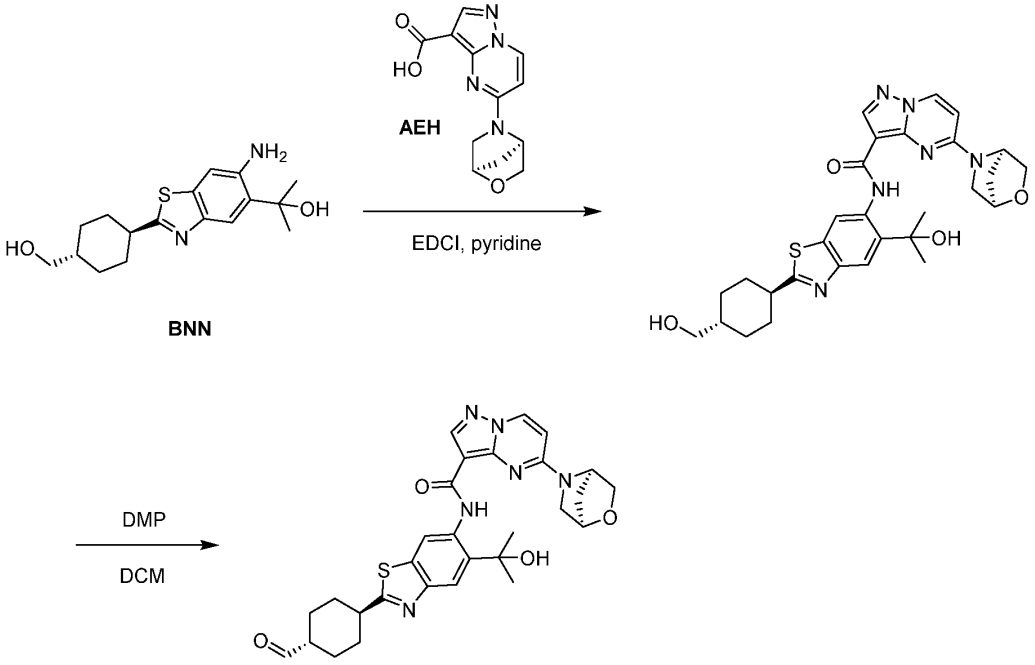
[001050] Step 3 - Methyl 6-amino-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazole-5-carboxylate

[001051] To a mixture of methyl 6-amino-2-[4-(benzyloxymethyl)cyclohexyl]-1,3-benzothiazole-5-carboxylate (1.70 g, 4.17 mmol) in THF (15 mL) and MeOH (15 mL) was added Pd/C (100 mg, 10 wt%), $Pd(OH)_2$/C (100 mg, 10 wt%) and HCl (12 M, 345 uL) under N_2. Then, the mixture was purged with H_2 three times and stirred under H_2 (15 psi) at 25 °C for 12 hours. On completion, the mixture was filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, PE: EA = 5:1 to 0:1) to give the title compound (850 mg, 64% yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.27 (s, 1H), 6.67 (s, 2H), 4.44 (t, *J* = 5.2 Hz, 1H), 3.84 (s, 3H), 3.26 (t, *J* = 5.6 Hz, 2H), 2.98 - 2.89 (m, 1H), 2.17 - 2.08 (m, 2H), 1.86 (dd, *J* = 2.4, 13.2 Hz, 2H), 1.56 - 1.46 (m, 2H), 1.44 - 1.36 (m, 1H), 1.12 - 1.02 (m, 2H).

[001052] Step 4 - 2-[6-Amino-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazol-5-yl]propan-2-ol

[001053] To a mixture of methyl 6-amino-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazole-5-carboxylate (600 mg, 1.87 mmol) in THF (5.0 mL) was added MeMgBr (3 M, 3.12 mL) at 0 °C. The mixture was then stirred at 25 °C for 3 hours. On completion, the mixture was quenched with water (60 mL) and the aqueous phase was extracted with ethyl acetate (3 x 30 mL).The combined organic phase was washed with brine (2 x 50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 3:1 to 0:1) to give the title compound (490 mg, 73% yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (s, 1H), 7.08 (s, 1H), 5.66 (s, 2H), 5.36 (s, 1H), 4.44 (t, *J* = 5.2 Hz, 1H), 3.26 (t, *J* = 5.6 Hz, 2H), 2.94 - 2.86 (m 1H), 2.15 - 2.08 (m, 2H), 1.87 - 1.83 (m, 2H), 1.57 (s, 6H), 1.54 - 1.47 (m, 2H), 1.43 - 1.39 (m, 1H), 1.12 - 1.01 (m, 2H).

[001054] N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (Intermediate BNO)



[001055] Step 1 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl] -5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

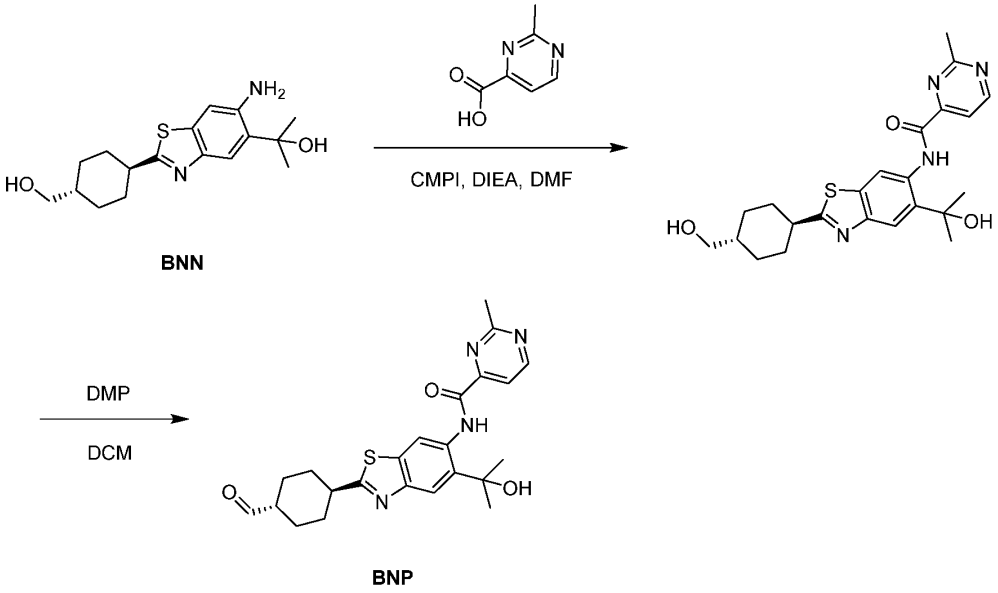
[001056] To a mixture of 2-[6-amino-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazol-5-yl]propan-2-ol (65.0 mg, 203 umol, Intermediate BNN) and 5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (58.1 mg, 223 umol, Intermediate AEH) in pyridine (5.0 mL) was added EDCI (46.7 mg, 243 umol). The reaction mixture was stirred at 25 °C for 1.5 hours. On completion, the mixture was quenched with water (1.0 mL) and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (55.0 mg, 48% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 - 10.51 (m, 1H), 8.76 (d, J = 7.6 Hz, 1H), 8.48 - 8.21 (m, 2H), 7.87 (s, 1H), 6.86 - 6.38 (m, 1H), 5.76 - 4.99 (m, 2H), 4.78 - 4.62 (m, 1H), 4.45 (s, 1H), 3.86 - 3.67 (m, 2H), 3.62 - 3.55 (m, 1H), 3.46 - 3.38 (m, 1H), 3.28 (s, 2H), 3.08 - 2.98 (m, 1H), 2.22 - 2.13 (m, 2H), 1.96 - 1.84 (m, 4H), 1.66 - 1.60 (m, 1H), 1.57 (s, 6H), 1.50 - 1.37 (m, 2H), 1.18 - 1.05 (m, 2H).

[001057] Step 2- N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide

[001058] To a mixture of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)- 1,3-

benzothiazol-6-yl]-5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (35.0 mg, 62.2 umol) in DCM (3.0 mL) was added $NaHCO_3$ (26.1 mg, 311 umol) and DMP (29.0 mg, 68.4 umol) at 0 °C. Then the mixture was stirred at 20 °C for 0.5 hour. On completion, the mixture was poured into the water (30 mL) and the aqueous phase was extracted with ethyl acetate (2 X 20 mL). The combined organic phase was washed with brine (2 x 20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (34.0 mg, 97% yield) as a brown solid. LC-MS (ESI^+) *m/z* 561.4 $(M+H)^+$.

[001059] N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-2-methyl- pyrimidine-4-carboxamide (Intermediate BNP)



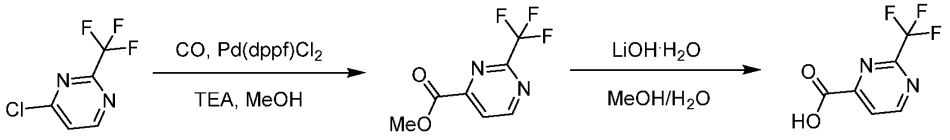
[001060] Step 1 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-2- methyl-pyrimidine-4-carboxamide

[001061] To a mixture of 2-[6-amino-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazol-5-yl]propan-2-ol (110 mg, 343 umol, Intermediate BNN) in DMF (5 mL) was added DIEA (133 mg, 1.03 mmol) and CMPI (105 mg, 412 umol, CAS# 45528-84-5). Then 2-methylpyrimidine-4-carboxylic acid (42.7 mg, 309 umol, CAS#13627-49-1) was added and the reaction mixture was stirred at 25 °C for 0.5 hour. On completion, the mixture was concentrated *in vacuo*. The residue was purified by reversed-phase HPLC (0.1% FA condition) to give the title compound (105 mg, 69% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 9.08 (s, 1H), 9.03 (d, J = 5.2 Hz, 1H), 7.97 (d, J = 5.2 Hz, 1H), 7.92 - 7.90 (m, 1H), 6.22 (s, 1H), 3.28 (d, J = 6.0 Hz, 2H), 3.04 - 3.00 (m, 1H), 2.78 (s, 3H), 2.22 - 2.14 (m, 2H), 1.91 - 1.87 (m, 2H), 1.66 (s, 6H), 1.61 (s, 4H), 1.42 (d, J = 2.8 Hz, 1H), 1.16 - 1.05 (m, 2H).

[001062] Step 2 - N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-2-methyl- pyrimidine-4-carboxamide

[001063] To a mixture of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-2-methyl-pyrimidine-4-carboxamide (25.0 mg, 56.7 umol) in DCM (10 mL) was added $NaHCO_3$ (23.8 mg, 284 umol) and DMP (28.9 mg, 68.1 umol). The reaction mixture was stirred at 25 °C for 0.5 hour. On completion, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (5 mL), diluted with water (80 mL), and extracted with DCM (2 x 60 mL). The combined organic phase was washed with brine (2 X 50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (24.0 mg, 96% yield) as a brown solid. LC-MS (ESI^+) *m/z* 439.3 $(M+H)^+$.

[001064] 2-(Trifluoromethyl)pyrimidine-4-carboxylic acid (Intermediate BIR)



BIR

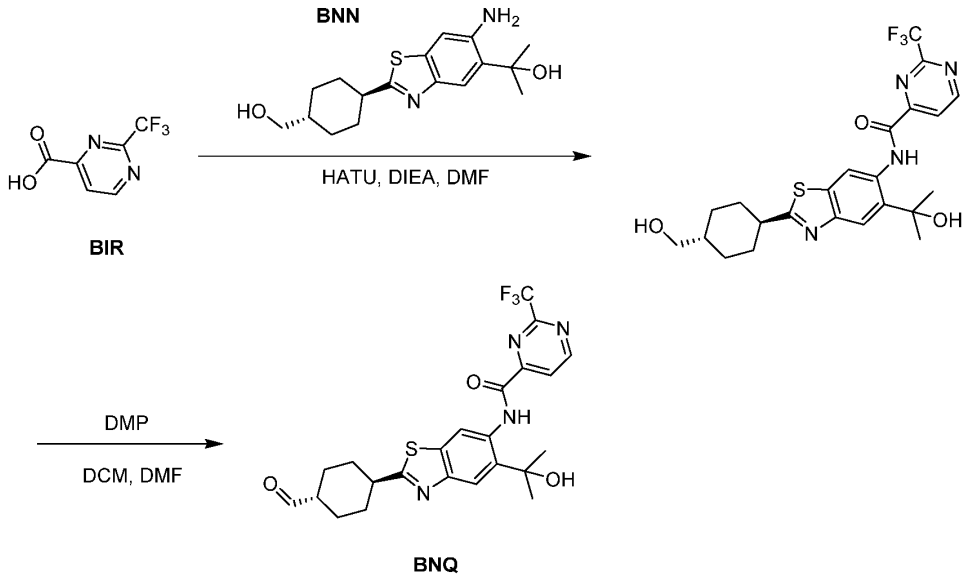
[001065] Step 1 - Methyl 2-(trifluoromethyl)pyrimidine-4-carboxylate

[001066] To a solution of 4-chloro-2-(trifluoromethyl)pyrimidine (100 mg, 547 umol, CAS# 1514-96-1) in MeOH (3 mL) was added $Pd(dppf)Cl_2$ (40.1 mg, 54.8 umol) and TEA (166 mg, 1.64 mmol, 228 uL) under N_2 atmosphere. The suspension was degassed and purged with CO for 3 times. The mixture was stirred under CO (50 Psi.) at 80 °C for 16 hrs. On completion, the reaction mixture was filtered and the filtrate concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=0/1 to 10/1, PE: EA = 5: 1, Rf = 0.24) to give the title compound (100 mg, 88% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$-*d*) δ 9.17 (d, *J* = 5.2 Hz, 1H), 8.20 (d, *J* = 4.8 Hz, 1H), 4.08 (s, 3H).

[001067] Step 2 - 2-(Trifluoromethyl)pyrimidine-4-carboxylic acid

[001068] To a solution of methyl 2-(trifluoromethyl)pyrimidine-4-carboxylate (70.0 mg, 339 umol) in MeOH (4.00 mL) and H_2O (0.40 mL) was added $LiOH·H_2O$ (42.7 mg, 1.02 mmol). The mixture was stirred at 20 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to remove MeOH, then acid by addition 1 N HCl until the pH = 3-4, then extracted with EA (3 X 5 mL). The combined organic layer was washed with brine (2 X 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (45.0 mg, 68% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.29 (d, *J* = 5.2 Hz, 1H), 8.26 (d, *J* = 4.8 Hz, 1H).

[001069] N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-2-(trifluoromethyl)pyrimidine-4-carboxamide (Intermediate BNQ)



[001070] Step 1 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]- 2-(trifluoromethyl)pyrimidine-4-carboxamide

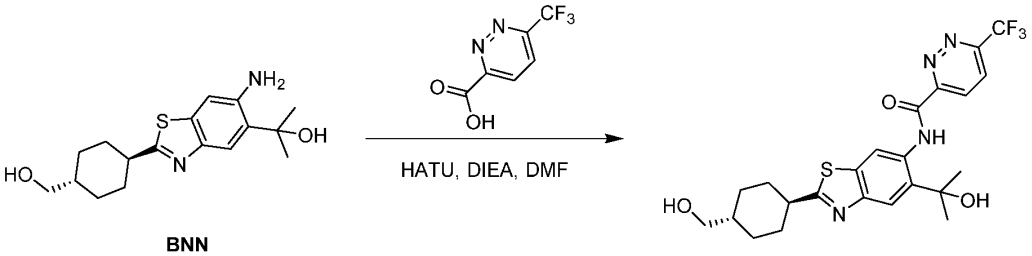
[001071] To a solution of 2-[6-amino-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazol-5-yl]propan-2-ol (100 mg, 312 umol, Intermediate BNN), 2-(trifluoromethyl)pyrimidine-4-carboxylic acid (54 mg, 280 umol, Intermediate BIR) in DMF (1.5 mL) was added DIEA (80.6 mg, 624 umol), and HATU (178 mg, 468 umol) and the mixture was stirred at 25 °C for 1 hour. On completion, the mixture was concentrated *in vacuo* to give the crude product. The crude product was purified by reverse phase flash (FA condition) to give the title compound as light yellow solid (80 mg, 50% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ9.28 (d, J = 3.2 Hz, 1H), 9.07 (s, 1H), 8.35 (d, J = 3.6 Hz, 1H), 7.83 (s, 1H), 4.57 - 4.34 (m, 1H), 3.27 (d, J = 6.4 Hz, 2H), 3.06 - 2.96 (m, 1H), 2.17 (d, J = 10.4 Hz, 2H), 1.92 - 1.83 (m, 2H), 1.60 (s, 6H), 1.58 (d, J = 3.2 Hz, 1H), 1.56 - 1.50 (m, 1H), 1.48 - 1.39 (m, 1H), 1.28 - 1.21 (m, 1H), 1.16 - 1.03 (m, 2H); LC-MS (ESI$^+$) m/z 495.2 $(M+H)^+$.

[001072] Step 2 - N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-2-(trifluoro methyl)pyrimidine-4-carboxamide

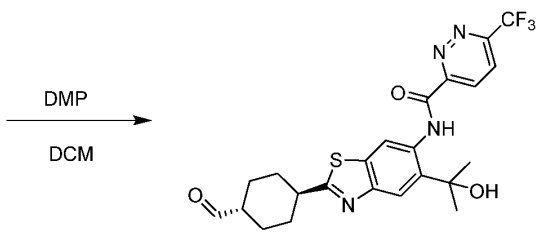
[001073] To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol- 6-yl]-2-(trifluoromethyl)pyrimidine-4-carboxamide (50 mg, 101 umol) in DCM (3 mL) and DMF (0.5 mL) was added DMP (64.3 mg, 151 umol) at 25 °C. The mixture was stirred at 25 °C for 2 hours. On completion, the reaction was quenched with $Na_2S_2O_3$ (0.5 mL) and $NaHCO_3$ (3 mL). The residue was diluted with water (15 mL), and extracted with DCM (40 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (48 mg, 96 % yield) as a white

solid. LC-MS (ESI^+) m/z 493.2 $(M+H)^+$.

[001074] N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoro methyl)pyridazine-3-carboxamide (Intermediate BNR)



BNN



BNR

[001075] Step 1 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl] -6-(trifluoromethyl)pyridazine-3-carboxamide

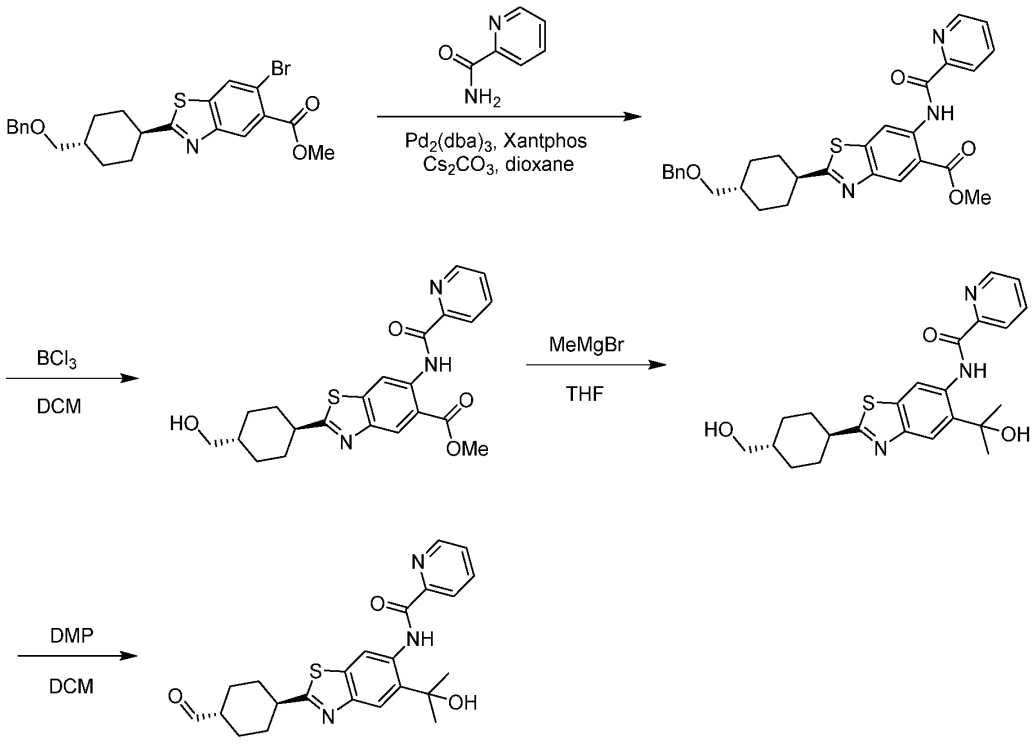
[001076] To a solution of 2-[6-amino-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazol-5-yl]propan-2-ol (100 mg, 312 umol, Intermediate BNN), 6-(trifluoromethyl)pyridazine-3-carboxylic acid (59.9 mg, 312 umol, CAS# 1192155-05-7) and DIEA (80.6 mg, 624 umol) in DMF (1 mL) was added HATU (177 mg, 468 umol) in DMF (1 mL). The reaction mixture was stirred at 25 °C for 2 hrs. The reaction mixture was then filtered and the filtrate was purified by reverse phase (0.1% FA) to give the title compound (110 mg, 71% yield) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 9.12 (s, 1H), 8.67 - 8.61 (m, 1H), 8.54 (d, J = 8.8 Hz, 1H), 7.92 (s, 1H), 6.43 (s, 1H), 4.46 (t, J = 5.2 Hz, 1H), 3.28 (t, J = 5.6 Hz, 2H), 3.05 (m, 1H), 2.22 - 2.15 (m, 2H), 1.89 (m, 2H), 1.67 (s, 6H), 1.63 - 1.54 (m, 2H), 1.45 (m, 1H), 1.11 (m, 2H).

[001077] Step 2 - N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoro methyl)pyridazine-3-carboxamide

[001078] To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol -6-y l]-6-(trifluoromethyl)pyridazine-3-carboxamide (90 mg, 181 umol) in DCM (1 mL) was added DMP (108 mg, 254 umol) and the reaction mixture was stirred at 25 °C for 1 hr. The reaction mixture was then quenched with sat. aq. $Na_2S_2O_3$ (1 mL), then sat. aq. $NaHCO_3$ was added until the pH = 7 ~ 8. The reaction mixture was diluted with water (10 mL), and extracted with DCM (3 x 10 mL). The combined

organic layer was washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (80.0 mg, 89% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 9.63 (s, 1H), 9.12 (s, 1H), 8.68 - 8.60 (m, 1H), 8.54 (d, J = 8.8 Hz, 1H), 7.92 (s, 1H), 6.43 (s, 1H), 3.14 - 3.06 (m, 1H), 2.42 - 2.38 (m, 1H), 2.27 - 2.21 (m, 2H), 2.11 - 2.05 (m, 2H), 1.69 - 1.63 (m, 8H), 1.45 - 1.37 (m, 2H).

[001079] N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]pyridine-2-carboxamide (Intermediate BJF)



BJF

[001080] Step 1 - Methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-(pyridine-2-carbonylamino)-1,3-benzothiazole- 5-carboxylate

[001081] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-bromo-1,3-benzothiazole-5-carboxylate (1.00 g, 2.11 mmol, synthesized via Steps 1-3 of Intermediate BAW) and pyridine-2-carboxamide (283 mg, 2.32 mmol, CAS# 1452-77-3) in dioxane (10 mL) was added Cs_2CO_3 (1.37 g, 4.22 mmol), Xantphos (243 mg, 421 umol) and $Pd_2(dba)_3$ (193 mg, 210 umol) at 25 °C. The reaction mixture was stirred at 80 °C for 48 hours under N_2. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 20: 1 to 3: 1) to give the title compound (750 mg, 55% yield) as yellow solid. LC-MS (ESI^+) m/z

516.1 $(M+H)^+$.

[001082] Step 2 - Methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-(pyridine-2-carbonylamino)-1,3-benzothiazole-5- carboxylate

[001083] To a solution of methyl 2-[4-(benzyloxymethyl)cyclohexyl]-6-(pyridine-2-carbonylamino)-1,3- benzothiazole-5-carboxylate (400 mg, 775 umol) in DCM (15 mL) was added BCl_3 (1 M, 1.55 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 4 hours. On completion, the reaction mixture was added of sat. aq. $NaHCO_3$ (3 mL), then the mixture was diluted with H_2O (50 mL) and extracted with EA (3 X 20 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 10: 1 to 1: 1) to give the title compound (230 mg, 69% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 13.19 (s, 1H), 9.59 (s, 1H), 8.81 (d, J = 4.0 Hz, 1H), 8.73 (s, 1H), 8.32 (d, J = 8.0 Hz, 1H), 7.98 - 7.88 (m, 1H), 7.55 - 7.46 (m, 1H), 7.27 (s, 1H), 4.06 (s, 3H), 3.55 (d, J = 6.0 Hz, 2H), 3.13 - 3.01 (m, 1H), 2.39 - 2.28 (m, 2H), 2.08 - 1.95 (m, 2H), 1.77 - 1.67 (m, 2H), 1.65 - 1.60 (m, 1H), 1.27 - 1.14 (m, 2H).

[001084] Step 3 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6- yl]pyridine-2-carboxamide

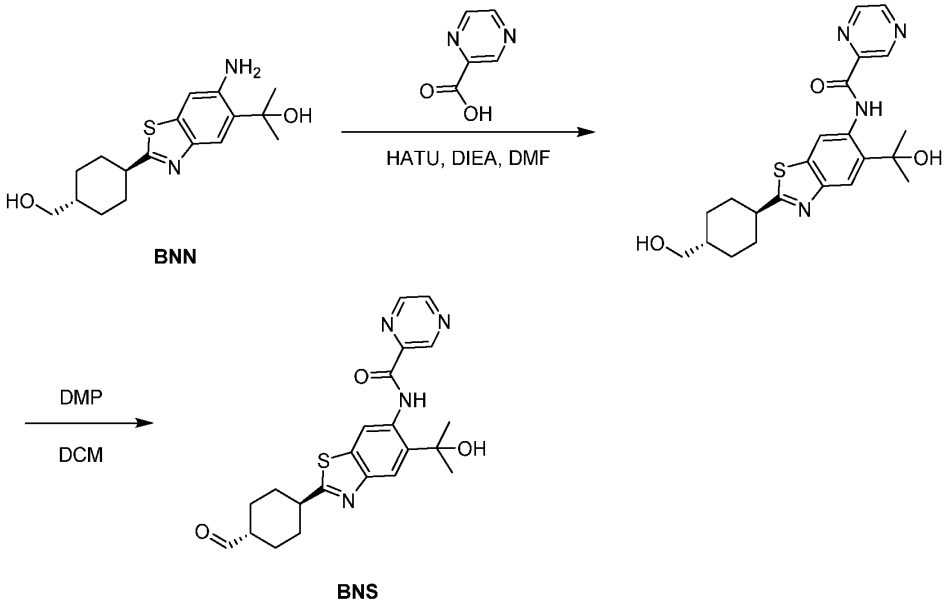
[001085] To a solution of methyl 2-[4-(hydroxymethyl)cyclohexyl]-6-(pyridine-2-carbonylamino)-1,3- benzothiazole-5-carboxylate (230 mg, 540 umol) in THF (6 mL) was added MeMgBr (3 M, 1.08 mL) at 0 °C. The mixture was stirred at 0 - 25 °C for 2 hours. On completion, the reaction mixture was quenched with sat.aq NH_4Cl (3 mL) at 0 °C, diluted with H_2O (30 mL) and extracted with EA (3 X 10 mL). The combined organic layers were washed by brine (20 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (125 mg, 54% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.52 (s, 1H), 9.05 (s, 1H), 8.75 - 8.70 (m, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.12 - 8.05 (m, 1H), 7.87 (s, 1H), 7.70 - 7.64 (m, 1H), 6.15 (s, 1H), 4.45 (t, J = 5.2 Hz, 1H), 3.30 - 3.25 (m, 2H), 3.08 - 2.98 (m, 1H), 2.21 - 2.14 (m, 2H), 1.92 - 1.83 (m, 2H), 1.63 (s, 6H), 1.60 - 1.51 (m, 2H), 1.48 - 1.40 (m, 1H), 1.16 - 1.05 (m, 2H); LC-MS (ESI^+) m/z 426.2 $(M+H)^+$.

[001086] Step 4 - N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]pyridine-2 -carboxamide

[001087] To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol -6-yl]pyridine-2-carboxamide (125 mg, 293 umol) in DCM (1.5 mL) was added DMP (161 mg, 381 umol) at 25 °C. The reaction mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (1 mL) and sat. aq. $NaHCO_3$ (1 mL), then diluted with H_2O (15 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (2 X 5

mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (120 mg, 96% yield) as yellow solid. LC-MS (ESI^+) m/z 406.2 $(M-17)^+$.

[001088] N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]pyrazine-2-carboxamide (Intermediate BNS)



[001089] Step 1 - N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl] pyrazine-2-carboxamide

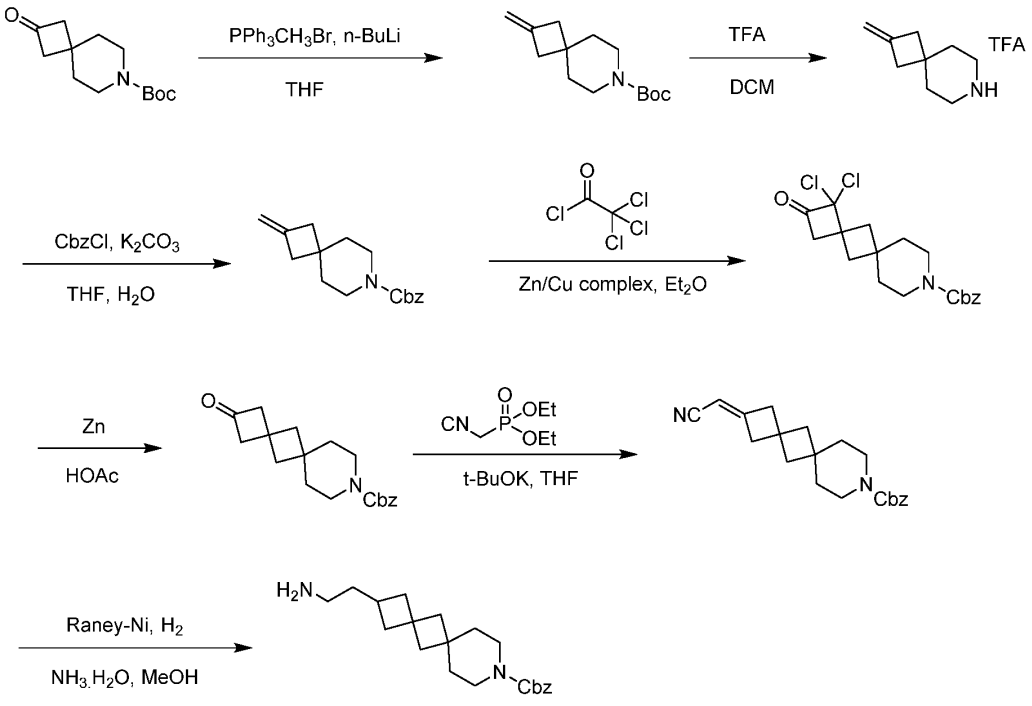
[001090] To a solution of 2-[6-amino-2-[4-(hydroxymethyl)cyclohexyl]-1,3-benzothiazol-5-yl]propan-2-ol (150 mg, 468 umol, Intermediate BNN) and pyrazine-2-carboxylic acid (52.3 mg, 421 umol, CAS #98-97-5) in DMF (5 mL) was added HATU (267 mg, 702 umol) and DIEA (121 mg, 936 umol) and the mixture was stirred at 25 °C for 1 hour. On completion, the mixture was concentrated *in vacuo*. The crude product was purified by reverse phase flash (FA condition) to give the title compound (138 mg, 68% yield) as white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 9.37 (d, J = 1.6 Hz, 1H), 9.05 (s, 1H), 8.94 (d, J = 2.4 Hz, 1H), 8.81 (dd, J = 1.6, 2.4 Hz, 1H), 7.89 (s, 1H), 6.28 (s, 1H), 4.45 (t, J = 5.2 Hz, 1H), 3.27 (t, J = 5.6 Hz, 2H), 3.04 (tt, J = 3.6, 12.0 Hz, 1H), 2.21 - 2.13 (m, 2H), 1.88 (dd, J = 2.8, 13.6 Hz, 2H), 1.63 (s, 6H), 1.59 - 1.51 (m, 2H), 1.49 - 1.38 (m, 1H), 1.17 - 1.03 (m, 2H) ; LC-MS (ESI^+) m/z 427.2 $(M+H)^+$.

[001091] Step 2 - N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]pyrazine-2- carboxamide

[001092] To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol- 6-yl]pyrazine-2-carboxamide (128 mg, 300 umol) in THF (2 mL) and DMF (0.5 mL) was

added DMP (191 mg, 450 umol) and the mixture was stirred at 25 °C for 1 hour. On completion, the reaction was quenched with sat. aq. $Na_2S_2O_3$ (2 mL) and sat. aq. $NaHCO_3$ (3 mL). The residue was diluted with water (20 mL), and extracted with EA (3 x 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (110 mg, 86% yield) as light brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 9.37 (d, J = 1.2 Hz, 1H), 9.08 - 9.03 (m, 1H), 8.93 (d, J = 2.4 Hz, 1H), 8.81 (d, J = 1.6 Hz, 1H), 7.90 - 7.89 (m, 1H), 3.69 (d, J = 4.8 Hz, 1H), 3.10 - 3.08 (m, 1H), 3.03 - 2.93 (m, 1H), 2.28 - 2.12 (m, 3H), 2.03 - 1.94 (m, 1H), 1.91 (s, 1H), 1.85 - 1.74 (m, 1H), 1.63 (s, 6H), 1.58 - 1.46 (m, 1H), 1.32 - 1.20 (m, 1H) ; LC-MS (ESI^+) m/z 425.2 $(M+H)^+$.

[001093] Benzyl 2-(2-aminoethyl)-9-azadispiro[3.1.56.14]dodecane-9-carboxylate (Intermediate BNT)



BNT

[001094] Step 1 - Tert-butyl 2-methylene-7-azaspiro[3.5]nonane-7-carboxylate

[001095] To a solution of methyl(triphenyl)phosphonium-bromide (19.4 g, 54.3 mmol) in THF (100 mL) was added t-BuOK (7.03 g, 62.6 mmol) at 0 °C dropwise. After the reaction mixture was stirred at 0 °C for 0.5 hr, a solution of tert-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (10.0 g, 41.7 mmol, CAS# 203661-69-2) in THF (30 mL) was added at 0 °C. Then the reaction mixture was warmed to 20 °C and stirred for 1 hr. On completion, the reaction mixture was poured into saturated NH_4Cl (200 mL) and extracted with EA (3 X 90 mL). The combined organic layers were washed with brine (2 x 50 mL), dried

over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 80: 1) to give the title compound (8.40 g, 84% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (d, *J* = 2.0 Hz, 2H), 3.39 - 3.25 (m, 4H), 2.43 (d, *J* = 1.2 Hz, 4H), 1.59 - 1.52 (m, 4H), 1.46 (s, 9H).

[001096] Step 2 - 2-Methylene-7-azaspiro[3.5]nonane

[001097] To a solution of tert-butyl 2-methylene-7-azaspiro[3.5]nonane-7-carboxylate (8.80 g, 37.0 mmol) in DCM (50 mL) was added TFA (30.8 g, 270 mmol, 20 mL). The reaction mixture was stirred at 10 °C for 0.5 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (9.00 g, 96% yield, TFA salt) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (br s, 2H), 4.97 - 4.89 (m, 2H), 3.19 (s, 4H), 2.54 (t, *J* = 2.4 Hz, 4H), 1.97 - 1.86 (m, 4H).

[001098] Step 3 - Benzyl 2-methylene-7-azaspiro[3.5]nonane-7-carboxylate

[001099] To a solution of 2-methylene-7-azaspiro[3.5]nonane (9.00 g, 35.8 mmol, TFA salt) and K_2CO_3 (9.90 g, 71.6 mmol) in a mixed solvents of THF (60 mL) and H_2O (20 mL) was added CbzCl (7.94 g, 46.5 mmol,). The reaction mixture was stirred at 10 °C for 2 hrs. On completion, the reaction mixture was diluted with water (80 mL) and extracted with EA (3 x 80 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 60: 1) to give the title compound (8.40 g, 86% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.28 (m, 5H), 5.13 (s, 2H), 4.84 (q, *J* = 2.4 Hz, 2H), 3.48 - 3.36 (m, 4H), 2.44 (t, *J* = 2.4 Hz, 4H), 1.63 - 1.55 (m, 4H).

[001100] Step 4 - Benzyl 3,3-dichloro-2-oxo-9-azadispiro[3.1.56.14]dodecane-9-carboxylate

[001101] To a solution of benzyl 2-methylene-7-azaspiro[3.5]nonane-7-carboxylate (4.00 g, 14.7 mmol) in Et_2O (60 mL) was added Zn-Cu (8.00 g, 14.7 mmol, CAS# 53801-63-1). Then 2,2,2-trichloroacetyl chloride (8.04 g, 44.2 mmol, CAS# 76-02-8) in Et_2O (60 mL) was added dropwise at 15 °C, and the reaction mixture was stirred at 15- 30 °C for 2 hrs. On completion, the reaction mixture was poured into saturated $NaHCO_3$ (100 mL) and filtered. The organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 12: 1) to give the title compound (4.00 g, 56% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.32 (m, 5H), 5.16 - 5.12 (m, 2H), 3.49 - 3.42 (m, 4H), 3.40 (s, 2H), 2.53 - 2.45 (m, 2H), 2.00 - 1.91 (m, 2H), 1.62 - 1.55 (m, 4H).

[001102] Step 5 - Benzyl 2-oxo-9-azadispiro[3.1.56.14]dodecane-9-carboxylate

[001103] To a solution of benzyl 3,3-dichloro-2-oxo-9-azadispiro[3.1.5^6.1^4]dodecane-9-carboxylate (4.60 g, 12.03 mmol) in AcOH (30 mL) was added Zn (3.15 g, 48.1 mmol) at 10 °C. Then the reaction mixture was stirred at 80 °C for 3 hrs. On completion, the reaction mixture was diluted with ethyl acetate (100mL) and poured into saturated $NaHCO_3$ (100 mL). The water phase was extracted with EA (3 x 50mL). The combined organic layers were washed with saturated $NaHCO_3$ (3 X 50 mL), brine (2 x 50 mL), dried

over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 10: 1) to give the title compound (2.00 g, 53% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.30 (m, 5H), 5.13 (s, 2H), 3.47 - 3.39 (m, 4H), 3.12 (s, 4H), 2.12 (s, 4H), 1.60 - 1.55 (m, 4H).

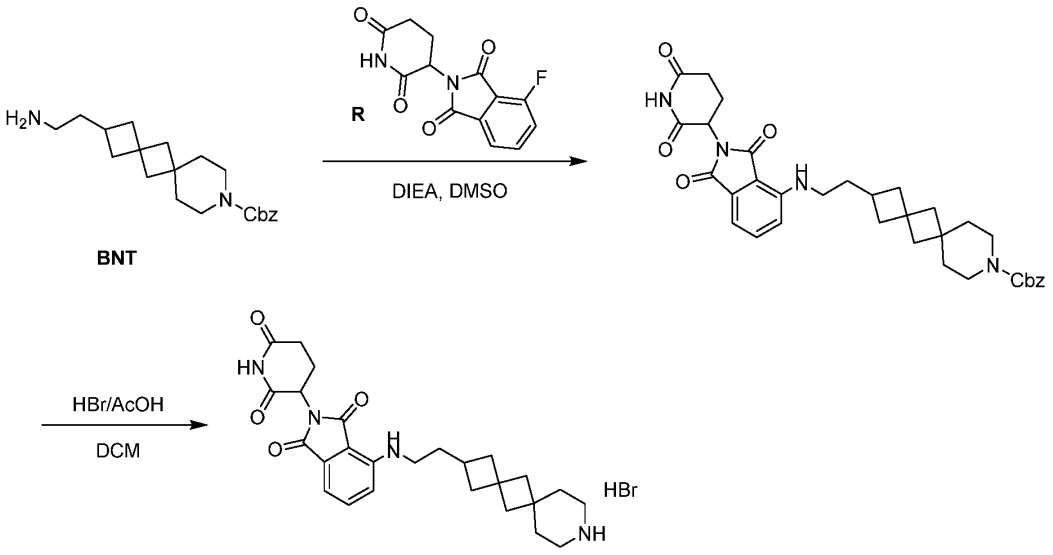
[001104] Step 6 - Benzyl 2-(cyanomethylene)-9-azadispiro[3.1.56.14]dodecane-9-carboxylate

[001105] To a solution of 2-diethoxyphosphorylacetonitrile (1.47 g, 8.30 mmol) (CAS# 2537-48-6) in THF (20 mL) was added t-BuOK (1.07 g, 9.57 mmol) at 0 °C. After the reaction mixture was stirred at 0 °C for thirty minutes, benzyl 2-oxo-9-azadispiro[3.1.5^6.1^4]dodecane-9-carboxylate (2.00 g, 6.38 mmol) in THF (10 mL) was added. The reaction mixture was stirred at 0 °C for 1 hr. On completion, the reaction mixture was poured into saturated NH_4Cl (50 mL) and extracted with ethyl acetate (3 X 60 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 10: 1) to give the title compound (1.85 g, 86% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.29 (m, 5H), 5.15 - 5.11 (m, 3H), 3.45 - 3.36 (m, 4H), 2.98 (d, J = 2.4 Hz, 2H), 2.87 (d, J = 2.0 Hz, 2H), 2.04 - 1.92 (m, 4H), 1.56 - 1.45(m, 4H).

[001106] Step 7 - Benzyl 2-(2-aminoethyl)-9-azadispiro[3.1.56.14]dodecane-9-carboxylate

[001107] To a solution of benzyl 2-(cyanomethylene)-9-azadispiro[3.1.5^6.1^4]dodecane-9-carboxylate (2.00 g, 5.94 mmol) and $NH_3{\cdot}H_2O$ (2.73 g, 21.8 mmol, 3 mL, 28% solution) in MeOH (30 mL) was added Raney-Ni (254 mg, 2.97 mmol). The reaction mixture was stirred at 25 °C for 6 hrs under H_2 (50 psi). On completion, the reaction mixture was filtered and the filter cake was washed with MeOH (50 mL). The filtrate was concentrated *in vacuo* to give the title compound (1.80 g, 88% yield) as blue oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 - 7.26 (m, 5H), 5.04 (s, 2H), 3.28 - 3.20(m, 4H), 2.54 - 2.51 (m, 2H), 2.17 - 2.00 (m, 3H), 1.85 (s, 2H), 1.81 - 1.44 (m, 6H), 1.43 - 1.33 (m, 4H).

[001108] 4-[2-(9-Azadispiro[3.1.56.14]dodecan-2-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline -1,3-dione (Intermediate BNU)



[001109] Step 1 - Benzyl 2-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]-9- azadispiro[3.1.56.14]dodecane-9-carboxylate

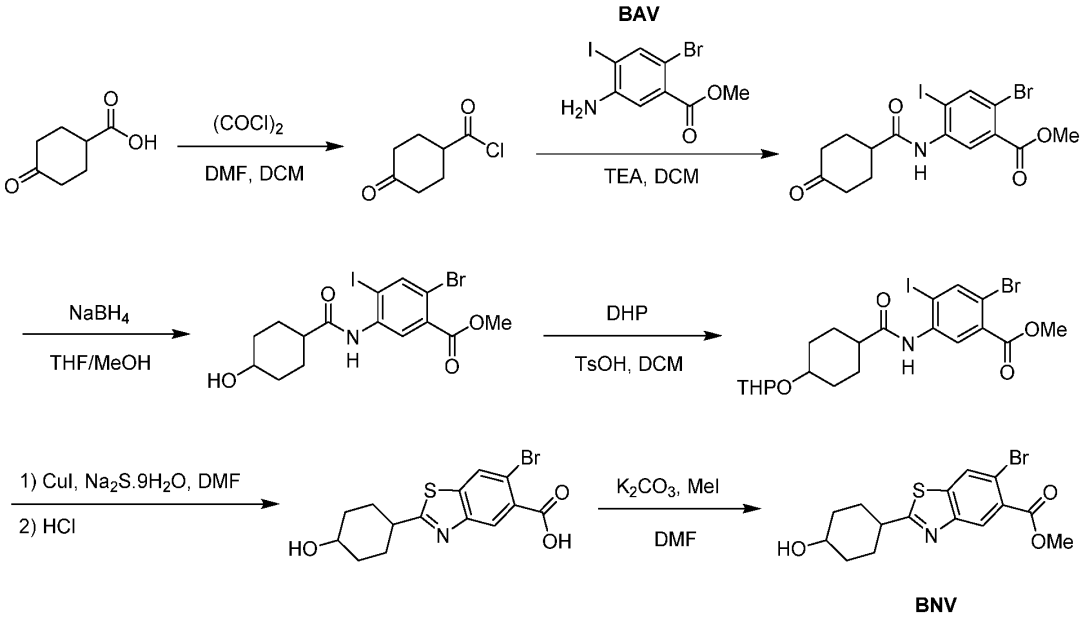
[001110] To a solution of benzyl 2-(2-aminoethyl)-9-azadispiro[3.1.5^6.1^4]dodecane-9-carboxylate (400 mg, 1.17 mmol, Intermediate BNT) and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (322 mg, 1.17 mmol, Intermediate R) in DMSO (5 mL) was added DIEA (301 mg, 2.34 mmol). The reaction mixture was stirred at 130 °C for 2 hrs. On completion, the reaction mixture was diluted with water (20 mL) and extracted with EA (3 X 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase (0.1% FA) to give the title compound (370 mg, 52% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.57 (dd, J = 7.2, 8.4 Hz, 1H), 7.40 - 7.26 (m, 5H), 7.09 - 6.97 (m, 2H), 6.50 - 6.40 (m, 1H), 5.09 - 4.99 (m, 3H), 3.28 (s, 4H), 3.23 - 3.13 (m, 2H), 2.96 - 2.81 (s, 1H), 2.62 - 2.51 (m, 2H), 2.23 - 1.98 (m, 4H), 1.86 (s, 2H), 1.74 (s, 2H), 1.71 - 1.59 (m, 4H), 1.46 - 1.34 (m, 4H).

[001111] Step 2 - 4-[2-(9-Azadispiro[3.1.56.14]dodecan-2-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline -1,3-dione

[001112] To a solution of benzyl 2-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]-9- azadispiro[3.1.5^6.1^4]dodecane-9-carboxylate (350 mg, 584 umol) in DCM (5 mL) was added HBr/AcOH (5 mL, 33% solution) and the reaction mixture was stirred at 20 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give a residue. The residue was dissolved in ACN/H_2O = 3/1 (30 mL) and lyophilized to give the title compound (310 mg, 97% yield, HBr salt) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.28 (br s, 2H), 7.58 (dd, J = 7.2, 8.4 Hz,

1H), 7.03 (dd, J = 8.0, 14.0 Hz, 2H), 6.68 - 6.20 (m, 1H), 5.04 (dd, J = 5.6, 12.8 Hz, 1H), 3.19 (t, J = 6.8 Hz, 2H), 2.99 - 2.82 (m, 5H), 2.64 - 2.51 (m, 2H), 2.23 - 1.97 (m, 4H), 1.92 - 1.89 (m, 3H), 1.79 (s, 2H), 1.73 -1.66 (m, 2H), 1.65 -1.63 (m, 1H), 1.62 - 1.57 (m, 4H).

[001113] Methyl 6-bromo-2-(4-hydroxycyclohexyl)benzo[d]thiazole-5-carboxylate (Intermediate BNV)



[001114] Step 1 - 4-Oxocyclohexanecarbonyl chloride

[001115] To a solution of 4-oxocyclohexanecarboxylic acid (4 g, 28.1 mmol, CAS# 874-61-3) in the DCM (20 mL) was added $(COCl)_2$ (5.36 g, 42.2 mmol, 3.69 mL) and DMF (411 mg, 5.63 mmol, 433 uL). The mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (4.5 g, 99% yield) as yellow oil, which was used in the next step directly.

[001116] Step 2 - Methyl-2-bromo-4-iodo-5-(4-oxocyclohexanecarboxamido)benzoate

[001117] To a solution of methyl 5-amino-2-bromo-4-iodo-benzoate (9.97 g, 28.0 mmol, Intermediate BAV) and TEA (8.51 g, 84.0 mmol, 11.7 mL) in the DCM (50 mL) was added 4-oxocyclohexanecarbonyl chloride (4.50 g, 28.0 mmol) and the mixture was stirred at 25 °C for 12 hrs. On completion, the reaction mixture was diluted with DCM (100 mL) and washed with saturated brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE: EA = 10:1 to 5:1) to give the title compound (4.00 g, 30% yield) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.11 (s, 1H), 7.57 (s, 1H), 3.94 (s, 3H), 2.82 - 2.79 (m, 1H), 2.65 - 2.57 (m, 2H), 2.50 - 2.40 (m, 2H), 2.39 - 2.30 (m, 2H), 2.21 - 2.09 (m, 2H).

[001118] Step 3 - Methyl 2-bromo-5-(4-hydroxycyclohexanecarboxamido)-4-iodobenzoate

[001119] To a solution of methyl 2-bromo-4-iodo-5-[(4-oxocyclohexanecarbonyl)amino]benzoate (3.20 g, 6.67 mmol) in the THF (50 mL) and MeOH (10 mL) was added $NaBH_4$ (252 mg, 6.67 mmol) in portions at 0 °C. The mixture was then stirred at 0 °C for 1 hr. On completion, the reaction mixture was quenched by water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (2.00 g, 62% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 12.0 Hz, 1H), 8.09 (s, 1H), 3.92 (s, 3H), 3.78 - 3.65 (m, 1H), 2.47 - 2.25 (m, 1H), 2.16 - 2.09 (m, 2H), 1.92 - 1.82 (m, 2H), 1.74 - 1.62 (m, 2H), 1.45 - 1.32 (m, 2H).

[001120] Step 4 - Methyl 2-bromo-4-iodo-5-(4-((tetrahydro-2H-pyran-2-yl)oxy) cyclohexanecarboxamido) benzoate

[001121] To a solution of methyl 2-bromo-5-[(4-hydroxycyclohexanecarbonyl)amino]-4-iodo-benzoate (2.00 g, 4.15 mmol) in the DCM (50 mL) was added TsOH (71.4 mg, 414 umol) and DHP (523 mg, 6.22 mmol, 569 uL) and the mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was diluted with DCM (100 mL) and washed with water (2 x 200 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EA=10/1 to 5/1) to give the title compound (1.24 g, 53% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 - 8.68 (m, 1H), 8.08 (s, 1H), 7.64 - 7.50 (m, 1H), 4.77 - 4.67 (m, 1H), 3.97 - 3.93 (m, 1H), 3.93 - 3.91 (m, 3H), 3.55 - 3.47 (m, 1H), 2.43 - 2.26 (m, 1H), 2.16 - 1.93 (m, 4H), 1.92 - 1.80 (m, 3H), 1.68 - 1.49 (m, 7H), 1.48 - 1.24 (m, 1H).

[001122] Step 5 - 6-Bromo-2-(4-hydroxycyclohexyl)benzo[d]thiazole-5-carboxylic acid

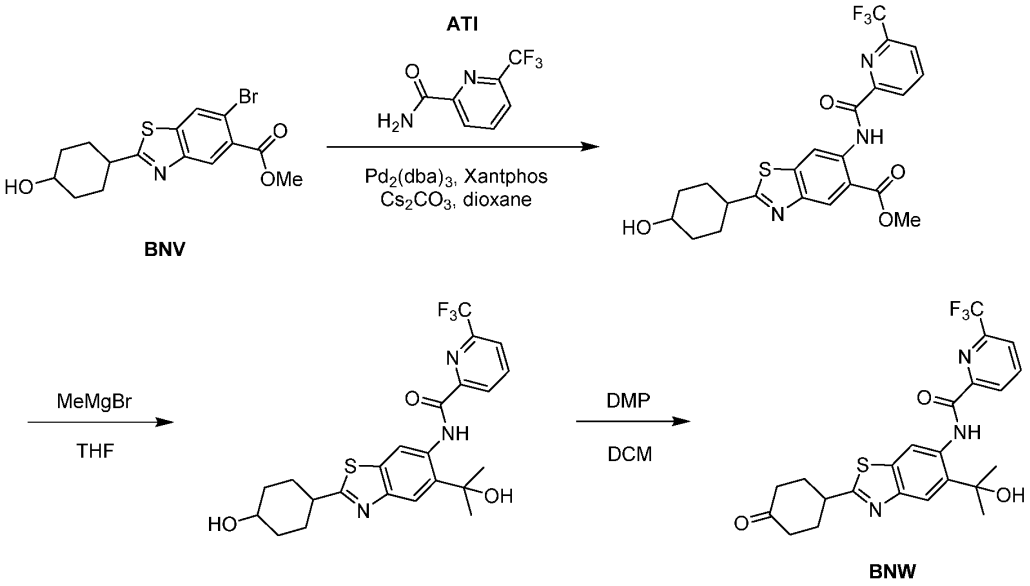
[001123] To a solution of methyl 2-bromo-4-iodo-5-[(4-tetrahydropyran-2-yloxycyclohexanecarbonyl) amino]benzoate (1.24 g, 2.19 mmol) in the DMF (12 mL) was added CuI (83.4 mg, 438 umol) and $Na_2S{\cdot}9H_2O$ (1.58 g, 6.57 mmol). Then the mixture was stirred at 80 °C for 12 hrs under N_2. Then the mixture was cooled to 25 °C and the HCl (12 M, 1.82 mL) was added and the mixture was stirred at 25 °C for 5 hrs. On completion, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (3 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (780 mg, 99% yield) as yellow solid. LC-MS (ESI^+) m/z 357.9 $(M+H)^+$.

[001124] Step 6 - Methyl 6-bromo-2-(4-hydroxycyclohexyl)benzo[d]thiazole-5-carboxylate

[001125] To a solution of 6-bromo-2-(4-hydroxycyclohexyl)-1,3-benzothiazole-5-carboxylic acid (780 mg, 2.19 mmol) in the DMF (10 mL) was added K_2CO_3 (605 mg, 4.38 mmol) and MeI (932 mg, 6.57 mmol, 409 uL) and the mixture was stirred at 25 °C for 12 hrs. On completion, the reaction mixture was diluted with EA (100 mL) and washed with water (3 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reversed phase flash (0.1% FA) to give the title compound (380 mg, 47% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.4 Hz,

1H), 8.15 (d, J = 3.2 Hz, 1H), 4.14 - 4.08 (m, 1H), 3.98 (s, 3H), 3.80 - 3.63 (m, 1H), 3.22 - 3.02 (m, 1H), 2.33 - 2.25 (m, 1H), 2.21 - 2.12 (m, 2H), 2.05 - 1.96 (m, 1H), 1.94 - 1.86 (m, 1H), 1.82 - 1.69 (m, 1H), 1.55 - 1.43 (m, 1H), 0.91 - 0.83 (m, 1H).

[001126] N-(5-(2-hydroxypropan-2-yl)-2-(4-oxocyclohexyl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide (Intermediate BNW)



[001127] Step 1 - 2-(4-Hydroxycyclohexyl)-6-(6-(trifluoromethyl)picolinamido)benzo[d]thiazole-5-carboxylic acid

[001128] A mixture of methyl 6-bromo-2-(4-hydroxycyclohexyl)-1,3-benzothiazole-5-carboxylate (320 mg, 864 umol, Intermediate BNV), 6-(trifluoromethyl)pyridine-2-carboxamide (164 mg, 864 umol, Intermediate ATI), $Pd_2(dba)_3$ (79.1 mg, 86.4 umol), Xantphos (100 mg, 173 umol) and Cs_2CO_3 (563 mg, 1.73 mmol) in the dioxane (1 mL) was stirred at 100 °C for 6 hrs under N_2. On completion, the mixture was filtered and concentrated *in vacuo* to give the title compound (400 mg, 99% yield) as yellow solid. LC-MS (ESI^+) m/z 480.0 $(M+H)^+$.

[001129] Step 2 - N-(2-(4-hydroxycyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoro methyl)picolinamide

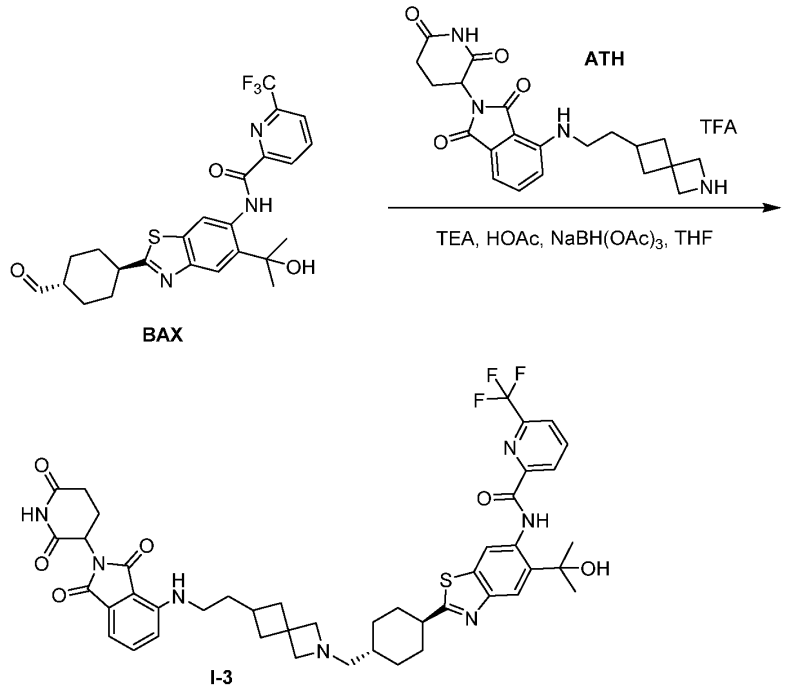
[001130] To a solution of methyl 2-(4-hydroxycyclohexyl)-6-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino] -1,3-benzothiazole-5-carboxylate (300 mg, 626 umol) in the THF (10 mL) was added MeMgBr (3 M, 2.09 mL) at -10 °C and the mixture was stirred at -10 °C for 3 hrs. On completion, the reaction mixture was quenched by ice water (50 mL) and extracted with EA (2 x 100 mL). Then the mixture was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (300 mg, 99% yield)

as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.43 (s, 1H), 9.20 (d, *J* = 1.6 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.14 (t, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 3.6 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 3.20 - 3.02 (m, 1H), 2.17 - 2.14 (m, 2H), 1.94 - 1.87 (m, 2H), 1.82 (d, *J* = 1.6 Hz, 6H), 1.78 - 1.74 (m, 2H), 1.51 - 1.49 (m, 2H), 0.89 - 0.87 (m, 1H).

[001131] Step 3 - N-(5-(2-hydroxypropan-2-yl)-2-(4-oxocyclohexyl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl) picolinamide

[001132] To a solution of N-[2-(4-hydroxycyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol -6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (300 mg, 626 umol) in the DCM (10 mL) was added DMP (398 mg, 938 umol, 290 uL) and the mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was quenched by the addition of $Na_2S_2O_3$ (aq. 20 mL) and $NaHCO_3$ (aq. 20 mL). Then the mixture was extracted with DCM (2 x 50 mL) and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EA=5/1 to 2/1) to give the title compound (240 mg, 80% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.46 (s, 1H), 9.21 (s, 1H), 8.50 (d, *J* = 7.6 Hz, 1H), 8.13 (t, *J* = 7.6 Hz, 1H), 7.98 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 3.60 - 3.51 (m, 1H), 2.61 - 2.49 (m, 6H), 2.30 - 2.22 (m, 2H), 1.82 (s, 6H), 0.91 - 0.82 (m, 1H).

Example 2 (Method 2). Synthesis of N-[2-[4-[[6-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]-2- azaspiro[3.3]heptan-2-yl]methyl]cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (I-3)



[001133] To a solution of 4-[2-(2-azaspiro[3.3]heptan-6-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline -1,3-dione (75.8 mg, 148 umol, TFA salt, Intermediate ATH) in THF (2 mL) was added TEA (15.0 mg, 148 umol), then the mixture stirred at 25 °C for 10 min. Next, HOAc (8.92 mg, 148 umol) and N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (73.0 mg, 148 umol, Intermediate BAX) were added to the mixture and the mixture was stirred at 25 °C for 20 minutes, then $NaBH(OAc)_3$ (62.9 mg, 297 umol) was added to the mixture at 0 °C. The reaction mixture was stirred at 0-25 °C for 2 hours. On completion, the reaction mixture was quenched with H_2O (1 mL) and concentrated *in vacuo*. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 um; mobile phase: [water(0.225%FA)-ACN]; B%: 31%-58%, 9 min) to give the title compound (59.1 mg, 41% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 11.09 (s, 1H), 9.06 (s, 1H), 8.49 - 8.44 (m, 1H), 8.38 (t, J = 8.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.88 (s, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.10 - 6.99 (m, 2H), 6.47 (t, J = 5.6 Hz, 1H), 6.07 (s, 1H), 5.05 (dd, J = 5.6, 12.8 Hz, 1H), 3.54 - 3.47 (m, 2H), 3.25 - 3.18 (m, 4H), 3.06 - 2.99 (m, 1H), 2.93 - 2.83 (m, 1H), 2.63 - 2.56 (m, 1H), 2.54 (s, 3H), 2.30 - 2.21 (m, 2H), 2.30 - 2.21 (m, 3H), 2.06 - 1.99 (m, 1H), 1.88 - 1.77 (m, 4H), 1.68 - 1.61 (m, 8H), 1.58 - 1.49 (m, 2H), 1.45 - 1.36 (m, 1H), 1.15 - 1.02 (m, 2H); LC-MS (ESI+) m/z 872.2 $(M+H)^+$.

Table 4: Compounds synthesized via Method 2 with the reductive amination of various intermediate

amines and aldehydes.

I-#	Inter-mediate Amine	Inter-mediate Aldehyde	LCMS (ES+) m/z $(M+H)^+$	^{1}HNMR (400MHz, DMSO-d_6) δ
I-4	AML	BCK	873.2	12.36 (s, 1H), 11.10 (s, 1H), 8.77 (s, 1H), 8.48 - 8.40 (m, 1H), 8.36 (t, *J* = 8.0 Hz, 1H), 8.20 - 8.11 (m, 1H), 7.64 - 7.51 (m, 1H), 7.41 (s, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 6.44 (d, *J* = 6.4 Hz, 1H), 5.97 - 5.92 (m, 1H), 5.05 (dd, *J* = 5.2, 12.4 Hz, 1H), 4.17 - 4.06 (m, 1H), 4.05 - 3.95 (m, 2H), 3.30 (s, 4H), 3.14 (t, *J* = 12.0 Hz, 2H), 2.95 - 2.82 (m, 1H), 2.63 - 2.54 (m, 2H), 2.27 - 2.16 (m, 2H), 2.14 - 2.08 (m, 2H), 2.06 - 2.00 (m, 1H), 1.81 (d, *J* = 10.8 Hz, 3H), 1.70 - 1.61 (m, 4H), 1.60 - 1.54 (m, 8H), 1.23 - 1.10 (m, 2H)
I-5	ATC	BAX	900.3	12.55 (s, 1H), 11.23 - 10.99 (m, 1H), 9.07 (s, 1H), 8.51 - 8.45 (m, 1H), 8.39 (t, *J* = 7.6 Hz, 1H), 8.19 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.89 (s, 1H), 7.59 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.14 - 6.99 (m, 2H), 6.48 (t, *J* = 6.0 Hz, 1H), 6.14 - 6.03 (m, 1H), 5.06 (dd, *J* = 5.6, 13.2 Hz, 1H), 3.31 (s, 2H), 3.23 (q, *J* = 6.4 Hz, 2H), 3.10 - 2.99 (m, 1H), 2.95 - 2.83 (m, 1H), 2.64 - 2.55 (m, 2H), 2.31 - 2.13 (m, 6H), 2.11 - 2.00 (m, 3H), 1.96 - 1.86 (m, 4H), 1.69 (q, *J* = 7.2 Hz, 2H), 1.64 (s, 6H), 1.61 - 1.53 (m, 4H), 1.47 (t, *J* = 5.2 Hz, 2H), 1.43 - 1.36 (m, 2H), 1.11 - 0.97 (m, 2H)
I-11	AUK		854.5	11.09 (s, 1H), 10.67 (s, 1H), 8.98 (s, 1H), 8.36 - 8.26 (m, 2H), 8.07 - 7.99 (m, 1H), 7.70 (s, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.62 - 6.50 (m, 1H), 5.05 (dd, *J* = 5.23, 12.8 Hz, 1H), 4.03 (s, 3H), 3.17 - 3.11 (m, 4H), 3.07 - 2.99 (m, 3H), 2.92 - 2.83 (m, 1H), 2.63 - 2.53 (m, 2H), 2.48 - 2.42 (m, 2H), 2.24 - 2.09 (m, 5H), 2.08 - 1.96 (m, 1H), 1.88 (t, *J* = 12.8 Hz, 4H), 1.70 - 1.48 (m, 5H), 1.44 - 1.28 (m, 3H), 1.19 - 0.88 (m, 4H)
I-12	ATC	BCK	818.5	11.09 (s, 1H), 10.72 (s, 1H), 9.02 (s, 1H), 8.03 - 7.93 (m, 2H), 7.67 (s, 1H), 7.63 - 7.52 (m, 2H), 7.14 - 6.96 (m, 2H), 6.47 (t, *J* = 6.0 Hz, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.04 (s, 3H), 3.23 - 3.18 (m, 2H), 3.05 - 2.97 (m, 1H), 2.93 - 2.83 (m, 1H), 2.62 (s, 3H), 2.61 - 2.52 (m, 2H), 2.32 - 2.09 (m, 7H), 2.09 - 2.00 (m, 3H), 1.94 - 1.83 (m, 4H), 1.72 - 1.63 (m, 2H), 1.61 - 1.49 (m, 5H), 1.48 - 1.42 (m, 2H), 1.42 - 1.34 (m, 2H), 1.10 - 0.94 (m, 2H)
I-13	BCM	BAX	886.4	12.54 (s, 1H), 11.20 - 10.97 (m, 1H), 9.06 (s, 1H), 8.46 (d, *J* = 7.6 Hz, 1H), 8.38 (t, *J* = 8.0 Hz, 1H), 8.21 - 8.16 (m, 1H), 7.92 - 7.86 (m, 1H), 7.64 - 7.55 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.50 (t, *J* = 5.6 Hz, 1H), 6.11 - 6.03 (m, 1H), 5.09 - 5.02 (m, 1H), 3.26 (d, *J* = 6.0 Hz, 2H), 3.09 (s, 2H), 3.07 - 2.99 (m, 1H), 2.98 (s, 2H), 2.93 - 2.81 (m, 1H), 2.63 - 2.56 (m, 2H), 2.22 - 2.09 (m, 7H), 2.09 - 1.95 (m, 2H), 1.84 (d, *J* = 9.6 Hz, 2H), 1.67 (s,

				2H), 1.63 (s, 6H), 1.57 - 1.45 (m, 4H), 1.42 - 1.35 (m, 2H), 1.33 - 1.21 (m, 1H), 1.12 - 0.96 (m, 2H)
I-14	BCR	BCN	886.0	11.10 (s, 1H), 10.51 (s, 1H), 9.00 (s, 1H), 8.51 - 8.46 (m, 1H), 8.46 - 8.39 (m, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.71 (s, 1H), 7.63 - 7.55 (m, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 6.8 Hz, 1H), 6.47 (t, *J* = 5.6 Hz, 1H), 5.06 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.03 (s, 3H), 3.06 - 3.00 (m, 1H), 2.93 - 2.85 (m, 1H), 2.64 - 2.57 (m, 4H), 2.19 (m, 3H), 2.16 (s, 3H), 2.06 - 2.01 (m, 1H), 1.95 - 1.88 (m, 3H), 1.83 - 1.74 (m, 2H), 1.66 - 1.42 (m, 9H), 1.34 - 1.11 (m, 5H), 1.09 - 0.98 (m, 2H)
I-15	AML	BCK	790.4	10.73 (s, 1H), 9.02 (s, 1H), 8.23 (s, 2H), 8.05 - 7.92 (m, 2H), 7.68 (s, 1H), 7.62 - 7.53 (m, 2H), 7.06 (d, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 6.4 Hz, 1H), 5. 05 (dd, *J* = 5.2 Hz , *J* = 12.4 Hz ,1H), 4.15 - 4.09 (m, 1H), 4.04 (s, 3H), 3.06 - 2.99 (m, 1H), 2.93 - 2.84 (m, 1H), 2.69 - 2.52 (m, 5H), 2.35 - 2.30 (m, 3H), 2.26 - 2.07 (m, 6H), 2.05 - 1.99 (m, 1H), 1.95 - 1.82 (m, 2H), 1.74 - 1.48 (m, 9H), 1.12 - 0.96 (m, 2H)
I-16	ATH	BCS	791.0	11.09 (s, 1H), 10.59 (s, 1H), 9.05 (d, *J* = 5.2 Hz, 1H), 8.98 (s, 1H), 7.97 (d, *J* = 5.2 Hz, 1H), 7.70 (s, 1H), 7.62 - 7.52 (m, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.47 (t, *J* = 5.6 Hz, 1H), 5.08 - 5.02 (m, 1H), 4.04 (s, 3H), 3.24 - 3.18 (m, 4H), 3.06 - 2.96 (m, 1H), 2.94 - 2.82 (m, 1H), 2.79 (s, 3H), 2.63 - 2.52 (m, 2H), 2.39 - 2.29 (m, 3H), 2.26 - 2.08 (m, 6H), 2.07 - 1.99 (m, 1H), 1.88 - 1.72 (m, 4H), 1.68 - 1.60 (m, 2H), 1.59 - 1.47 (m, 2H), 1.42 - 1.27 (m, 1H), 1.12 - 0.99 (m, 2H)
I-17	ATC	BCS	819.3	11.09 (s, 1H), 10.58 (s, 1H), 9.07 - 9.02 (m, 1H), 8.99 - 8.95 (m, 1H), 7.97 (d, *J* = 3.2 Hz, 1H), 7.70 (s, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.47 (s, 1H), 5.09 - 5.01 (m, 1H), 4.04 (s, 3H), 3.21 (d, *J* = 5.4 Hz, 2H), 3.07 - 2.96 (m, 1H), 2.93 - 2.83 (m, 1H), 2.79 (s, 3H), 2.63 - 2.52 (m, 2H), 2.31 - 2.11 (m, 7H), 2.09 - 2.00 (m, 3H), 1.95 - 1.83 (m, 4H), 1.68 (d, *J* = 7.2 Hz, 2H), 1.54 (s, 5H), 1.46 (s, 2H), 1.38 (t, *J* = 9.6 Hz, 2H), 1.10 - 0.93 (m, 2H)
I-18	ATC	BCK	901.3	12.37 (s, 1H), 11.10 (s, 1H), 8.90 - 8.70 (m, 1H), 8.48 - 8.42 (m, 1H), 8.37 (t, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 7.59 (dd, *J* = 7.6, 8.8 Hz, 1H), 7.42 (s, 1H), 7.05 (dd, *J* = 7.2, 19.6 Hz, 2H), 6.49 (t, *J* = 5.6 Hz, 1H), 5.97 - 5.90 (m, 1H), 5.06 (dd, *J* = 5.6, 13.2 Hz, 1H), 4.01 (d, *J* = 12.0 Hz, 2H), 3.26 - 3.21 (m, 2H), 3.20 - 3.10 (m, 3H), 2.95 - 2.85 (m, 1H), 2.64 - 2.54 (m, 3H), 2.31 - 2.21 (m, 3H),2.20 - 2.15 (m, 2H), 2.07 - 2.00 (m, 1H), 1.98 - 1.90 (m, 2H), 1.85 - 1.77 (m, 3H), 1.74 - 1.67 (m, 2H), 1.59 (s, 6H), 1.58 - 1.55 (m, 2H), 1.52 - 1.47 (m, 2H), 1.44 - 1.37 (m, 2H), 1.24 - 1.11 (m, 2H)
I-19	ATC	BCV	868.1	11.10 (s, 1H), 10.68 (s, 1H), 8.99 (s, 1H), 8.36 - 8.27 (m, 2H), 8.04 (dd, *J* = 1.6, 6.8 Hz, 1H), 7.70 (s, 1H), 7.62 -

				7.55 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.48 (t, *J* = 5.6 Hz, 1H), 5.06 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.04 (s, 3H), 3.26 - 3.19 (m, 2H), 3.07 - 2.98 (m, 1H), 2.91 - 2.83 (m, 1H), 2.64 - 2.56 (m, 1H), 2.30 - 2.14 (m, 9H), 2.09 (d, *J* = 6.8 Hz, 2H), 2.06 - 2.00 (m, 1H), 1.96 - 1.84 (m, 4H), 1.69 (q, *J* = 6.8 Hz, 2H), 1.61 - 1.51 (m, 5H), 1.47 (t, *J* = 5.0 Hz, 2H), 1.43 - 1.34 (m, 2H), 1.11 - 0.97 (m, 2H)
I-20	AUK	BCN	858.5	11.09 (s, 1H), 10.51 (s, 1H), 9.01 (s, 1H), 8.53 - 8.38 (m, 2H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.74 - 7.67 (m, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.64 - 6.53 (m, 1H), 5.05 (dd, *J* = 5.6, 12.6 Hz, 1H), 4.03 (s, 3H), 3.73 - 3.61 (m, 1H), 3.30 (s, 4H), 3.15 (d, *J* = 6.0 Hz, 2H), 3.09 - 3.00 (m, 1H), 2.94 - 2.83 (m, 2H), 2.61 (d, *J* = 2.4 Hz, 1H), 2.19 (d, *J* = 11.6 Hz, 2H), 2.10 - 1.92 (m, 4H), 1.91 - 1.81 (m, 2H), 1.70 - 1.51 (m, 6H), 1.45 - 1.35 (m, 2H), 1.23 - 1.07 (m, 2H), 1.05 - 0.93 (m, 2H)
I-21	BDG	BCN	886.3	11.10 (s, 1H), 10.49 (s, 1H), 9.03 - 8.95 (m, 1H), 8.50 - 8.37 (m, 2H), 8.27 - 8.20 (m, 1H), 7.69 (s, 1H), 7.57 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.45 (s, 1H), 5.05 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.02 (s, 3H), 3.33 - 3.30 (m, 2H), 3.06 - 2.97 (m, 1H), 2.94 - 2.83 (m, 1H), 2.64 - 2.56 (m, 3H), 2.27 - 2.18 (m, 4H), 2.16 (s, 3H), 2.15- 2.12 (m, 1H), 2.07 - 1.98 (m, 1H), 1.96 - 1.85 (m, 3H), 1.83 - 1.72 (m, 2H), 1.68 - 1.58 (m, 2H), 1.57 - 1.49 (m, 4H), 1.48 - 1.38 (m, 2H), 1.32 - 1.22 (m, 3H), 1.21 - 1.11 (m, 1H), 1.09-0.94 (m, 2H)
I-22	ATC	BCW	846.3	12.59 (s, 1H), 11.09 (s, 1H), 9.06 (s, 1H), 8.01 - 7.91 (m, 2H), 7.87 (s, 1H), 7.58 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.52 (dd, *J* = 0.8, 7.2 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.47 (t, *J* = 5.6 Hz, 1H), 6.14 - 5.95 (m, 1H), 5.05 (dd, *J* = 5.6, 12.8 Hz, 1H), 3.23 - 3.20 (m, 2H), 3.02 (t, *J* = 12.0 Hz, 2H), 2.92 - 2.84 (m, 1H), 2.61 (s, 3H), 2.58 - 2.52 (m, 2H), 2.30 - 2.22 (m, 3H), 2.19 - 2.12 (m, 3H), 2.11 - 2.07 (m, 2H), 2.06 - 1.99 (m, 1H), 1.95 - 1.86 (m, 4H), 1.72 - 1.67 (m, 2H), 1.64 (s, 6H), 1.60 - 1.50 (m, 5H), 1.47 (t, *J* = 5.2 Hz, 2H), 1.42 - 1.35 (m, 2H), 1.09 - 0.97 (m, 2H)
I-23	AOV	BCW	806.2	12.60 (s, 1H), 11.09 (s, 1H), 9.07 (s, 1H), 8.01 - 7.91 (m, 2H), 7.87 (s, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.16 (d, *J* = 8.4 Hz, 1H), 6.04 (s, 1H), 5.07 - 5.02 (m, 1H), 3.09 - 3.02 (m, 1H), 2.93 - 2.83 (m, 1H), 2.61 (s, 3H), 2.32 (m, 2H), 2.27 (s, 3H), 2.18 (m, 2H), 2.08 - 2.00 (m, 3H), 1.93 (m, 2H), 1.80 (m, 2H), 1.65 (s, 6H), 1.63 - 1.52 (m, 3H), 1.50 - 1.39 (m, 2H), 1.37 - 1.26 (m, 2H), 1.11 - 0.99 (m, 2H)
I-24	AVB	BAX	860.2	12.54 (s, 1H), 11.19 - 10.93 (m, 1H), 9.06 (s, 1H), 8.49 - 8.44 (m, 1H), 8.38 (t, *J* = 8.0 Hz, 1H), 8.18 (dd, *J* = 0.8,

				7.6 Hz, 1H), 7.89 (s, 1H), 7.59 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.49 (t, *J* = 5.6 Hz, 1H), 6.23 - 5.91 (m, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.31 - 3.30 (m, 2H), 3.11 - 2.97 (m, 1H), 2.94 - 2.75 (m, 3H), 2.63 - 2.54 (m, 2H), 2.20 - 2.12 (m, 2H), 2.12 - 2.08 (m, 2H), 2.06 - 1.99 (m, 1H), 1.94 - 1.86 (m, 2H), 1.86 - 1.78 (m, 2H), 1.72 - 1.65 (m, 2H), 1.63 (s, 6H), 1.60 - 1.48 (m, 5H), 1.37 - 1.28 (m, 1H), 1.25 - 1.13 (m, 2H), 1.11 - 0.96 (m, 2H)
I-25	BDG	BAX	914.4	12.53 (s, 1H), 11.54 - 10.56 (m, 1H), 9.06 (s, 1H), 8.49 - 8.44 (m, 1H), 8.38 (t, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.58 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.46 (t, *J* = 6.0 Hz, 1H), 5.04 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.31 - 3.31 (m, 2H), 3.10 - 2.96 (m, 1H), 2.94 - 2.81 (m, 1H), 2.63 - 2.56 (m, 1H), 2.54 - 2.52 (m, 2H), 2.24 - 2.16 (m, 4H), 2.14 (s, 3H), 2.14 - 2.11 (m, 1H), 2.08 - 1.98 (m, 1H), 1.96 - 1.85 (m, 3H), 1.83 - 1.72 (m, 2H), 1.69 - 1.64 (m, 1H), 1.63 (s, 6H), 1.59 - 1.50 (m, 4H), 1.50 - 1.40 (m, 3H), 1.33 - 1.24 (m, 2H), 1.24 - 1.12 (m, 2H), 1.07 - 0.95 (m, 2H)
I-26	APB	BAX	858.5	12.55 (s, 1H), 11.10 (s, 1H), 9.06 (s, 1H), 8.51 - 8.43 (m, 1H), 8.42 - 8.34 (m, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.92 - 7.83 (m, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.56 (br s, 1H), 6.12 - 6.04 (m, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.80 - 3.69 (m, 3H), 3.31 - 3.30 (m, 2H), 3.09 - 2.99 (m, 1H), 2.93 - 2.84 (m, 1H), 2.73 (s, 1H), 2.64 - 2.53 (m, 2H), 2.44 - 2.37 (m, 1H), 2.31 - 2.23 (m, 2H), 2.16 (d, *J* = 12.0 Hz, 2H), 2.07 - 1.90 (m, 4H), 1.88 - 1.80 (m, 2H), 1.63 (s, 6H), 1.62 - 1.49 (m, 4H), 1.20 - 1.05 (m, 2H)
I-27	BND	BAX	888.5	12.54 (s, 1H), 11.23 - 10.94 (m, 1H), 9.06 (s, 1H), 8.51 - 8.43 (m, 1H), 8.38 (t, *J* = 7.6 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.89 (s, 1H), 7.63 - 7.54 (m, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.51 - 6.44 (m, 1H), 6.16 - 5.95 (m, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.10 - 2.99 (m, 1H), 2.95 - 2.83 (m, 1H), 2.64 - 2.53 (m, 2H), 2.35 - 2.23 (m, 2H), 2.21 (d, *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 2.15 - 2.11 (m, 2H), 2.07 - 1.99 (m, 1H), 1.91 (d, *J* = 10.8 Hz, 2H), 1.86 - 1.78 (m, 2H), 1.72 (d, *J* = 11.6 Hz, 2H), 1.63 (s, 6H), 1.60 - 1.43 (m, 5H), 1.36 - 1.11 (m, 4H), 1.08 - 0.91 (m, 4H)
I-28	AOV	BAX	860.3	12.54 (s, 1H), 11.41 - 10.74 (m, 1H), 9.07 (s, 1H), 8.50 - 8.43 (m, 1H), 8.38 (t, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.89 (s, 1H), 7.58 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.15 (d, *J* = 8.4 Hz, 1H), 5.04 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.55 - 3.45 (m, 1H), 3.30 (s, 2H), 3.10 - 3.01 (m, 1H), 2.92 - 2.82 (m, 1H), 2.44 - 2.35 (m, 2H), 2.24 (d, *J* = 7.2 Hz, 2H), 2.22 - 2.15 (m, 5H), 2.08 - 1.99 (m, 3H), 1.93 (d, *J* = 11.2 Hz, 2H),

				1.80 - 1.72 (m, 2H), 1.63 (s, 6H), 1.60 - 1.52 (m, 2H), 1.51 - 1.37 (m, 3H), 1.35 - 1.23 (m, 2H), 1.11 - 0.98 (m, 2H)
I-29	AJF	BAX	886.3	12.54 (s, 1H), 11.09 (s, 1H), 9.06 (s, 1H), 8.53 - 8.30 (m, 2H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.93 - 7.84 (m, 1H), 7.57 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.14 - 7.08 (m, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.56 (t, *J* = 6.0 Hz, 1H), 6.16 - 5.97 (m, 1H), 5.05 (dd, *J* = 5.6, 12.8 Hz, 1H), 3.15 (t, *J* = 6.0 Hz, 2H), 3.07 - 2.98 (m, 1H), 2.92 - 2.87 (m, 2H), 2.84 - 2.79 (m, 2H), 2.27 (d, *J* = 6.8 Hz, 2H), 2.20 - 2.10 (m, 2H), 2.08 - 1.97 (m, 2H), 1.91 - 1.83 (m, 4H), 1.63 (s, 9H), 1.57 - 1.48 (m, 3H), 1.41 - 1.27 (m, 4H), 1.13 - 0.97 (m, 4H)
I-30	AUK	BAX	886.3	12.54 (s, 1H), 11.09 (s, 1H), 9.06 (s, 1H), 8.51 - 8.43 (m, 1H), 8.42 - 8.35 (m, 1H), 8.19 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.88 (s, 1H), 7.57 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.46 (t, *J* = 5.6 Hz, 1H), 6.12 - 6.02 (m, 1H), 5.05 (dd, *J* = 5.4, 12.8 Hz, 1H), 3.10 - 2.97 (m, 1H), 2.95 - 2.81 (m, 1H), 2.63 - 2.55 (m, 2H), 2.29 - 2.11 (m, 6H), 2.09 - 1.99 (m, 4H), 1.93 - 1.82 (m, 5H), 1.63 (s, 6H), 1.60 - 1.54 (m, 5H), 1.53 - 1.45 (m, 5H), 1.08 - 0.98 (m, 2H)
I-31	BFJ	BAX	886.4	12.54 (s, 1H), 11.22 - 10.89 (m, 1H), 9.06 (s, 1H), 8.49 - 8.44 (m, 1H), 8.38 (t, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 7.91 - 7.86 (m, 1H), 7.62 - 7.53 (m, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.47 (t, *J* = 5.6 Hz, 1H), 6.08 - 6.04 (m, 1H), 5.10 - 5.02 (m, 1H), 3.24 - 3.15 (m, 1H), 3.14 - 3.08 (m, 2H), 3.08 - 2.91 (m, 4H), 2.90 - 2.81 (m, 1H), 2.63 - 2.51 (m, 2H), 2.23 - 2.07 (m, 6H), 2.06 - 1.98 (m, 1H), 1.96 - 1.88 (m, 1H), 1.87 - 1.79 (m, 3H), 1.78 - 1.71 (m, 1H), 1.63 (s, 6H), 1.58 - 1.44 (m, 2H), 1.38 - 1.19 (m, 2H), 1.11 - 0.97 (m, 2H), 0.81 (d, *J* = 6.4 Hz, 3H)
I-32	BFI	BAX	886.4	12.54 (s, 1H), 11.39 - 10.60 (m, 1H), 9.06 (s, 1H), 8.50 - 8.43 (m, 1H), 8.38 (d, *J* = 7.6 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.91 - 7.85 (m, 1H), 7.62 - 7.55 (m, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.47 (t, *J* = 5.6 Hz, 1H), 5.08 - 5.03 (m, 1H), 3.23 - 3.16 (m, 1H), 3.12 (s, 2H), 3.09 - 3.00 (m, 2H), 2.99 - 2.94 (m, 2H), 2.64 - 2.52 (m, 2H), 2.25 - 2.10 (m, 6H), 2.08 - 1.90 (m, 3H), 1.85 (d, *J* = 10.8 Hz, 3H), 1.80 - 1.72 (m, 1H), 1.63 (s, 6H), 1.60 - 1.48 (m, 3H), 1.35 - 1.20 (m, 2H), 1.12 - 0.97 (m, 2H), 0.81 (d, *J* = 6.4 Hz, 3H)
I-33	ATH	BNF	836.5	12.65 (s, 1H), 11.09 (s, 1H), 9.05 (s, 1H), 7.89 - 7.86 (m, 1H), 7.77 (dd, *J* = 2.0, 9.2 Hz, 1H), 7.58 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.49 (dd, *J* = 2.4, 9.6 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.48 (t, *J* = 6.0 Hz, 1H), 6.12 - 6.07 (m, 1H), 5.05 (dd, *J* = 5.6, 12.8 Hz, 1H), 3.44 (d, *J* = 2.0 Hz, 4H), 3.22 (d, *J* = 5.6 Hz, 2H), 3.06 - 2.98 (m, 1H), 2.92 - 2.84 (m, 1H), 2.63 (s, 3H), 2.59 (s, 1H), 2.28 - 2.22 (m, 2H), 2.19 - 2.12 (m, 3H), 2.05 - 2.00 (m,

				1H), 1.88 - 1.76 (m, 5H), 1.64 (s, 9H), 1.61 - 1.49 (m, 3H), 1.43 - 1.34 (m, 1H), 1.16 - 1.02 (m, 2H)
I-34[a]	AML	BNH	816.4	($CDCl_3$) 10.50 (s, 1H), 9.15 (s, 1H), 8.84 (d, *J* = 6.8 Hz, 1H), 8.80 (s, 1H), 8.77 (d, *J* = 2.8 Hz, 1H), 8.00 - 7.94 (m, 1H), 7.53 (s, 1H), 7.49 (t, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.07 (dd, *J* = 4.4, 6.8 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.31 (d, *J* = 5.6 Hz, 1H), 4.96 - 4.89 (m, 1H), 4.07 (s, 3H), 4.06 - 4.00 (m, 1H), 3.09 - 2.99 (m, 1H), 2.95 - 2.88 (m, 1H), 2.85 - 2.72 (m, 2H), 2.52 - 2.50 (m, 2H), 2.47 - 2.40 (m, 3H), 2.34 - 2.24 (m, 4H), 2.18 - 2.12 (m, 1H), 2.07 - 1.97 (m, 2H), 1.78 - 1.63 (m, 10H), 1.21 - 1.07 (m, 2H)
I-35	AJF	BCK	887.3	12.36 (s, 1H), 11.09 (s, 1H), 8.80 - 8.75 (m, 1H), 8.46 - 8.41 (m, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.20 - 8.16 (m, 1H), 7.57 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.41 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 5.6 Hz, 1H), 5.98 - 5.90 (m, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.99 (d, *J* = 12.4 Hz, 2H), 3.31 (s, 2H), 3.13 (d, *J* = 11.6 Hz, 3H), 2.95 - 2.82 (m, 1H), 2.64 - 2.53 (m, 2H), 2.31 - 2.14 (m, 4H), 2.15 - 2.08 (m, 2H), 2.07 - 1.98 (m, 1H), 1.90 - 1.75 (m, 5H), 1.58 (s, 6H), 1.51 - 1.46 (m, 6H), 1.22 - 1.08 (m, 2H)
I-36	ATH	BCK	873.3	12.36 (s, 1H), 11.10 (s, 1H), 8.81 - 8.73 (m, 1H), 8.47 - 8.41 (m, 1H), 8.40 - 8.32 (m, 1H), 8.20 - 8.12 (m, 1H), 7.58 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.41 (s, 1H), 7.12 - 6.98 (m, 2H), 6.47 (d, *J* = 5.6 Hz, 1H), 5.97 - 5.91 (m, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.00 (d, *J* = 12.8 Hz, 2H), 3.93 - 3.64 (m, 4H), 3.26 - 3.19 (m, 2H), 3.13 (d, *J* = 11.6 Hz, 2H), 2.95 - 2.75 (m, 3H), 2.64 - 2.52 (m, 2H), 2.36 - 2.25 (m, 2H), 2.17 (dd, *J* = 7.6, 15.2 Hz, 1H), 2.08 - 1.95 (m, 1H), 1.88 - 1.85 (m, 2H), 1.75 (d, *J* = 10.8 Hz, 3H), 1.65 (d, *J* = 6.8 Hz, 2H), 1.58 (s, 6H), 1.31 - 1.16 (m, 2H)
I-37	ATH	BFQ	819.4	12.40 (s, 1H), 11.08 (s, 1H), 8.77 (s, 1H), 8.00 - 7.89 (m, 2H), 7.58 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.49 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.40 (s, 1H), 7.10 - 6.98 (m, 2H), 6.47 (t, *J* = 6.0 Hz, 1H), 5.93 - 5.87 (m, 1H), 5.05 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.05 - 3.91 (m, 2H); 3.24 - 3.18 (m, 2H), 3.14 - 3.04 (m, 4H), 3.01 (s, 2H), 2.94 - 2.83 (m, 1H), 2.62 - 2.56 (m, 5H), 2.24 - 2.12 (m, 5H), 2.06 - 1.99 (m, 1H), 1.79 - 1.71 (m, 4H), 1.68 - 1.62 (m, 2H), 1.59 (s, 6H), 1.54 - 1.47 (m, 1H), 1.22 - 1.09 (m, 2H)
I-38	AJF	BFS	859.3	12.37 (s, 1H), 11.10 (s, 1H), 8.79 (s, 1H), 8.46 - 8.42 (m, 1H), 8.41 - 8.34 (m, 1H), 8.17 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.58 (dd, *J* = 7.6, 8.4 Hz, 1H), 7.46 (s, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.47 (*t*, *J* = 5.6 Hz, 1H), 5.99 - 5.93 (m, 1H), 5.10 - 5.01 (m, 1H), 4.18 (t, *J* = 8.0 Hz, 2H), 3.75 (dd, *J* = 5.6, 8.0 Hz, 2H), 3.07 - 3.02 (m, 1H), 2.92 - 2.84 (m, 1H), 2.61 (m, 1H), 2.59 - 2.52 (m, 7H), 2.31 - 2.20 (m, 3H), 2.07 - 2.00 (m, 1H), 1.91 - 1.83

				(m, 2H), 1.58 (s, 6H), 1.57 - 1.54 (m, 2H), 1.53 - 1.47 (m, 4H)
I-39	AQS	BCN	874.2	11.10 (s, 1H), 10.49 (s, 1H), 9.02 - 8.92 (m, 1H), 8.50 - 8.45 (m, 1H), 8.44 - 8.38 (m, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.70 (s, 1H), 7.62 - 7.55 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 6.8 Hz, 1H), 5.06 (dd, *J* = 5.2, 12.8 Hz, 1H), 4.02 (s, 3H), 3.91 - 3.82 (m, 1H), 3.77 - 3.67 (m, 1H), 3.08 - 2.97 (m, 1H), 2.94 - 2.77 (m, 4H), 2.67 (s, 2H), 2.34 - 2.31 (m, 1H), 2.19 - 2.09 (m, 4H), 2.06 - 1.98 (m, 3H), 1.93 - 1.72 (m, 7H), 1.63 - 1.53 (m, 3H), 1.48 - 1.37 (m, 2H), 1.11 - 0.97 (m, 2H)
I-40	ATH	BFT	827.2	11.10 (s, 1H), 8.33 - 8.30 (m, 1H), 8.22 (s, 1H), 7.91 (s, 1H), 7.79 - 7.69 (m, 2H), 7.62 - 7.51 (m, 2H), 7.39 - 7.32 (m, 1H), 7.04 (dd, *J* = 8.4, 19.6 Hz, 2H), 6.68 (d, *J* = 7.2 Hz, 1H), 6.51 - 6.43 (m, 1H), 5.21 - 5.12 (m, 1H), 5.10 - 5.01 (m, 1H), 3.45 (s, 2H), 3.21 (s, 2H), 3.11 (s, 2H), 2.92 - 2.83 (m, 1H), 2.62 - 2.59 (m, 1H), 2.27 (d, *J* = 6.4 Hz, 2H), 2.25 - 2.11 (m, 6H), 2.07 - 1.98 (m, 2H), 1.85 (d, *J* = 10.4 Hz, 2H), 1.80 - 1.73 (m, 2H), 1.68 - 1.60 (m, 3H), 1.58 - 1.50 (m, 2H), 1.35 (d, *J* = 8.8 Hz, 6H), 1.16 - 1.05 (m, 2H)
I-41	AVZ	BAX	874.1	12.54 (s, 1H), 11.10 (s, 1H), 9.06 (s, 1H), 8.50 - 8.43 (m, 1H), 8.38 (t, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.88 (s, 1H), 7.57 (dd, *J* = 7.2, 8.0 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.57 (t, *J* = 5.6 Hz, 1H), 6.07 (s, 1H), 5.05 (dd, *J* = 5.2, 13.2 Hz, 1H), 3.16 (t, *J* = 6.4 Hz, 2H), 3.07 - 3.00 (m, 1H), 2.94 - 2.83 (m, 1H), 2.63 - 2.52 (m, 2H), 2.22 (d, *J* = 6.0 Hz, 2H), 2.17 (s, 3H), 2.17 - 2.11 (m, 2H), 2.07 - 2.01 (m, 1H), 1.94 - 1.87 (m, 2H), 1.85 - 1.79 (m, 2H), 1.77 - 1.71 (m, 2H), 1.63 (s, 6H), 1.60 - 1.44 (m, 5H), 1.28 - 1.16 (m, 2H), 1.07 - 0.97 (m, 4H)
I-42[a]	ATH	BNI	799.2	($CDCl_3$) 8.47 (d, *J* = 7.6 Hz, 1H), 8.40 - 7.95 (m, 1H), 7.79 (s, 1H), 7.72 - 7.66 (m, 1H), 7.63 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.55 - 7.48 (m, 2H), 7.11 (d, *J* = 6.8 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.56 (d, *J* = 7.2 Hz, 1H), 6.16 (t, *J* = 5.2 Hz, 1H), 4.95 - 4.88 (m, 1H), 3.86 (s, 3H), 3.63 (s, 2H), 3.52 (s, 2H), 3.23 - 3.16 (m, 2H), 3.04 (tt, *J* = 3.6, 12.0 Hz, 1H), 2.94 - 2.81 (m, 2H), 2.81 - 2.69 (m, 2H), 2.59 (d, *J* = 6.4 Hz, 2H), 2.43 - 2.36 (m, 2H), 2.28 (d, *J* = 8.0 Hz, 2H), 2.18 - 2.12 (m, 1H), 1.98 (d, *J* = 11.6 Hz, 2H), 1.88 (dd, *J* = 8.4, 12.4 Hz, 2H), 1.77 - 1.71 (m, 2H), 1.71 - 1.63 (m, 2H), 1.62 (d, *J* = 2.8 Hz, 1H), 1.16 (dq, *J* = 3.2, 12.6 Hz, 2H)
I-43	ATH	BGW	873.5	12.62 (s, 1H), 11.08 (s, 1H), 9.49 (s, 1H), 8.51 - 8.43 (m, 1H), 8.43 - 8.35 (m, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 7.62 - 7.54 (m, 1H), 7.04 (dd, *J* = 8.0, 20.0 Hz, 2H), 6.52 - 6.45 (m, 1H), 6.36 (s, 1H), 5.05 (dd, *J* = 5.2, 13.2 Hz, 1H), 3.25 - 3.17 (m, 2H), 3.16 - 2.95 (m, 4H), 2.94 - 2.81 (m, 1H), 2.65 - 2.54 (m, 2H), 2.23 - 2.10 (m, 7H), 2.08 - 1.96 (m,

				2H), 1.89 - 1.80 (m, 2H), 1.79 - 1.70 (m, 2H), 1.68 - 1.47 (m, 9H), 1.26 - 1.17 (m, 2H), 1.12 - 0.97 (m, 2H)
I-44	APB	BFS	831.3	12.36 (s, 1H), 11.18 - 11.02 (m, 1H), 8.78 (s, 1H), 8.46 - 8.41 (m, 1H), 8.36 (t, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.45 (s, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.55 - 6.49 (m, 1H), 5.98 - 5.91 (m, 1H), 5.05 (dd, *J* = 5.6, 12.8 Hz, 1H), 4.13 (t, *J* = 8.0 Hz, 2H), 3.74 (dd, *J* = 6.0, 7.8 Hz, 2H), 3.15 (s, 2H), 3.09 (s, 2H), 2.95 - 2.82 (m, 1H), 2.81 - 2.71 (m, 1H), 2.63 - 2.54 (m, 5H), 2.44 - 2.40 (m, 2H), 2.20 - 2.14 (m, 2H), 2.06 - 2.00 (m, 1H), 1.89 - 1.81 (m, 2H), 1.57 (s, 6H)
I-45	BGX	BAX	832.5	12.54 (s, 1H), 11.09 (s, 1H), 9.06 (s, 1H), 8.51 - 8.44 (m, 1H), 8.38 (t, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.91 - 7.87 (m, 1H), 7.64 - 7.52 (m, 1H), 7.16 - 7.06 (m, 1H), 7.06 - 6.98 (m, 1H), 6.65 - 6.46 (m, 1H), 6.18 - 5.93 (m, 1H), 5.11 - 5.01 (m, 1H), 3.68 - 3.49 (m, 2H), 3.42 (t, *J* = 7.2 Hz, 2H), 3.29 - 3.24 (m, 2H), 3.07 - 2.97 (m, 1H), 2.95 - 2.77 (m, 3H), 2.63 - 2.52 (m, 2H), 2.36 - 2.28 (m, 2H), 2.14 (d, *J* = 12.0 Hz, 2H), 2.05 - 1.99 (m, 1H), 1.88 - 1.77 (m, 3H), 1.63 (s, 6H), 1.59 - 1.49 (m, 2H), 1.42 - 1.30 (m, 1H), 1.21 - 0.90 (m, 2H)
I-46	BGZ	BAX	888.6	12.54 (s, 1H), 11.33 - 10.88 (m, 1H), 9.06 (s, 1H), 8.49 - 8.44 (m, 1H), 8.38 (t, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.91 - 7.86 (m, 1H), 7.64 - 7.55 (m, 1H), 7.13 - 7.06 (m, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.52 (t, *J* = 5.6 Hz, 1H), 6.18 - 5.97 (m, 1H), 5.08 - 5.01 (m, 1H), 3.09 - 3.00 (m, 1H), 2.92 - 2.83 (m, 1H), 2.61 - 2.56 (m, 3H), 2.26 - 2.13 (m, 9H), 2.05 - 1.99 (m, 1H), 1.96 - 1.88 (m, 2H), 1.63 (s, 6H), 1.62 - 1.51 (m, 9H), 1.50 - 1.39 (m, 5H), 1.08 - 0.98 (m, 2H)
I-47	ATH	BHA	854.3	12.70 (s, 1H), 11.09 (s, 1H), 9.08 (s, 1H), 8.39 - 8.27 (m, 2H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.90 - 7.87 (m, 1H), 7.58 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.20 - 6.87 (m, 3H), 6.47 (t, *J* = 5.6 Hz, 1H), 6.30 - 5.89 (m, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.21 (s, 4H), 3.11 (s, 2H), 3.05 - 2.97 (m, 1H), 2.93 - 2.83 (m, 1H), 2.63 - 2.51 (m, 2H), 2.27 (d, *J* = 6.4 Hz, 2H), 2.24 - 2.10 (m, 5H), 2.06 - 1.98 (m, 1H), 1.84 (d, *J* = 12.0 Hz, 2H), 1.79 - 1.72 (m, 2H), 1.65 (s, 6H), 1.63 (s, 2H), 1.59 - 1.48 (m, 2H), 1.39 - 1.28 (m, 1H), 1.13 - 0.97 (m, 2H)
I-48	AZA	BAX	874.2	12.55 (s, 1H), 11.09 (s, 1H), 9.07 (s, 1H), 8.50 - 8.44 (m, 1H), 8.38 (t, *J* = 8.0 Hz, 1H), 8.19 (dd, *J* = 0.7, 7.8 Hz, 1H), 7.89 (s, 1H), 7.58 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.59 (t, *J* = 6.0 Hz, 1H), 6.07 (s, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.30 - 3.26 (m, 2H), 3.09 - 3.00 (m, 1H), 2.93 - 2.81 (m, 1H), 2.63 - 2.51 (m, 2H), 2.30 - 2.20 (m, 3H), 2.18 (s, 3H), 2.17 - 2.11 (m, 2H), 2.07 - 1.99 (m, 1H), 1.97 - 1.88 (m, 2H), 1.87 - 1.79 (m, 1H), 1.70 - 1.62 (m, 8H), 1.61 - 1.49 (m, 5H), 1.49 - 1.39 (m, 4H), 1.09 - 0.98 (m, 2H)

I-49	ATH	BNK	827.4	11.11 - 11.03 (m, 1H), 8.28 (s, 1H), 7.76 (s, 1H), 7.63 - 7.54 (m, 2H), 7.51 - 7.46 (m, 1H), 7.27 - 7.17 (m, 2H), 7.15 - 7.10 (m, 1H), 7.08 - 6.98 (m, 2H), 6.46 (t, *J* = 5.6 Hz, 1H), 5.04 (dd, *J* = 5.6, 12.8 Hz, 1H), 3.91 - 3.80 (m, 1H), 3.22 - 3.17 (m, 3H), 3.15 - 3.09 (m, 2H), 3.05 - 2.99 (m, 3H), 2.96 - 2.82 (m, 3H), 2.62 - 2.53 (m, 1H), 2.24 - 1.93 (m, 9H), 1.83 - 1.81 (m, 2H), 1.77 - 1.69 (m, 5H), 1.64 - 1.62 (m, 2H), 1.56 - 1.44 (m, 2H), 1.42 - 1.35 (m, 3H), 1.34 - 1.24 (m, 4H), 1.09 - 0.95 (m, 2H)
I-50	ATH	BNM	867.5	11.91 (s, 1H), 11.09 (s, 1H), 9.01 (s, 1H), 8.35 (s, 1H), 8.10 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.91 - 7.88 (m, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.76 - 7.70 (m, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.04 (dd, *J* = 7.6, 18.4 Hz, 2H), 6.47 (t, *J* = 5.6 Hz, 1H), 5.07 - 5.03 (m, 1H), 3.21 (d, *J* = 5.6 Hz, 3H), 3.14 (s, 2H), 3.04 (s, 2H), 3.03 - 2.95 (m, 1H), 2.93 - 2.83 (m, 1H), 2.59 (d, *J* = 17.2 Hz, 1H), 2.23 - 2.12 (m, 6H), 2.09 - 1.97 (m, 5H), 1.84 (d, *J* = 10.8 Hz, 2H), 1.78 - 1.71 (m, 2H), 1.65 (s, 6H), 1.64 - 1.60 (m, 2H), 1.58 - 1.48 (m, 2H), 1.34 - 1.22 (m, 1H), 1.12 - 0.98 (m, 2H)
I-51	ATH	BNP	819.6	12.76 (s, 1H), 11.15 - 10.90 (m, 1H), 9.07 - 9.01 (m, 1H), 7.97 (d, *J* = 5.2 Hz, 1H), 7.89 (s, 1H), 7.62 - 7.55 (m, 1H), 7.09 - 7.05 (m, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.52 - 6.43 (m, 1H), 6.27 - 6.14 (m, 1H), 5.08 - 5.03 (m, 1H), 3.24 - 3.20 (m, 3H), 3.11 (s, 2H), 3.01 (s, 2H), 2.91 - 2.83 (m, 2H), 2.78 (s, 3H), 2.65 - 2.55 (m, 4H), 2.24 - 2.11 (m, 6H), 2.07 - 1.99 (m, 1H), 1.91 - 1.80 (m, 2H), 1.80 - 1.72 (m, 2H), 1.65 (s, 6H), 1.61 - 1.45 (m, 2H), 1.43 - 1.14 (m, 2H), 1.12 - 0.98 (m, 2H)
I-53	ATH	BHB	871.5	11.97 (s, 1H), 11.09 (s, 1H), 9.01 (s, 1H), 8.23 - 8.17 (m, 2H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.92 - 7.83 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.11 - 6.99 (m, 2H), 6.82 - 6.64 (m, 1H), 6.51 - 6.43 (m, 1H), 5.09 - 5.01 (m, 1H), 3.65 (s, 2H), 3.54 (s, 2H), 3.22 (d, *J* = 5.6 Hz, 2H), 3.03 (t, *J* = 12.4 Hz, 1H), 2.93 - 2.83 (m, 1H), 2.65 - 2.60 (m, 2H), 2.58 - 2.52 (m, 2H), 2.32 - 2.24 (m, 2H), 2.20 - 2.20 (m, 3H), 2.07 - 1.97 (m, 1H), 1.88 - 1.79 (m, 4H), 1.66 (s, 6H), 1.66 - 1.60 (m, 2H), 1.60 - 1.49 (m, 2H), 1.49 - 1.39 (m, 1H), 1.17 - 1.02 (m, 2H)
I-54	ATH	BNQ	873.4	12.74 (s, 1H), 11.09 (s, 1H), 9.38 (d, *J* = 5.2 Hz, 1H), 9.08 (s, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 7.90 (s, 1H), 7.59 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.11 - 6.99 (m, 2H), 6.47 (t, *J* = 5.6 Hz, 1H), 6.22 (s, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.69 (d, J = 8.0 Hz, 2H), 3.59 (d, *J* = 2.0 Hz, 2H), 3.24 - 3.19 (m, 2H), 3.10 - 2.99 (m, 1H), 2.94 - 2.83 (m, 1H), 2.68 - 2.65 (m, 1H), 2.63 - 2.53 (m, 2H), 2.32 - 2.24 (m, 2H), 2.16 (d, *J* = 8.4 Hz, 3H), 2.07 - 1.99 (m, 1H), 1.88 - 1.80 (m, 4H), 1.69 - 1.60 (m, 9H), 1.59 - 1.50 (m, 2H), 1.50 - 1.42 (m, 1H), 1.18 - 1.03 (m, 2H)
I-55	ATH	BNR	873.5	13.02 (s, 1H), 11.09 (s, 1H), 9.13 - 9.07 (m, 1H), 8.67 - 8.61 (m, 1H), 8.53 (d, *J* = 8.8 Hz, 1H), 7.93 - 7.88 (m, 1H),

				7.58 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.07 (dd, *J* = 8.4 Hz, 1H), 7.07 (dd, *J* = 7.2 Hz, 1H), 6.48 (t, *J* = 5.6 Hz, 1H), 6.42 (s, 1H), 5.09 - 5.00 (m, 1H), 3.21 (d, *J* = 7.2 Hz, 2H), 3.17 (s, 2H), 3.07 (s, 2H), 3.05 - 2.98 (m, 1H), 2.93 - 2.83 (m, 1H), 2.63 - 2.54 (m, 1H), 2.52 (s, 2H), 2.24 - 2.12 (m, 6H), 2.05 - 1.99 (m, 1H), 1.85 (M), 1.79 - 1.72 (m, 2H), 1.66 (s, 6H), 1.64 - 1.47 (m, 4H), 1.13 - 0.98 (m, 2H)
I-56	ATH	BHC	868.5	12.61 (s, 1H), 11.10 (s, 1H), 9.12 (s, 1H), 8.35 - 8.26 (m, 2H), 8.00 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.90 (s, 1H), 7.64 - 7.52 (m, 1H), 7.11 - 6.99 (m, 2H), 6.48 (t, *J* = 4.8 Hz, 1H), 6.22 (s, 1H), 5.06 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.27 - 3.20 (m, 5H), 3.15 (s, 2H), 3.07 - 2.98 (m, 1H), 2.94 - 2.84 (m, 1H), 2.63 - 2.53 (m, 3H), 2.32 - 2.28 (m, 2H), 2.27 - 2.25 (m, 1H), 2.24 - 2.12 (m, 6H), 2.08 - 1.99 (m, 1H), 1.90 - 1.73 (m, 4H), 1.67 - 1.62 (m, 7H), 1.60 - 1.49 (m, 2H), 1.41 - 1.27 (m, 1H), 1.12 - 1.00 (m, 2H)
I-57	ATH	BJF	804.4	12.52 (s, 1H), 11.10 (s, 1H), 9.04 (s, 1H), 8.75 - 8.68 (m, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 8.11 - 8.05 (m, 1H), 7.88 - 7.85 (m, 1H), 7.69 - 7.64 (m, 1H), 7.61 - 7.55 (m, 1H), 7.11 - 6.98 (m, 2H), 6.48 (t, *J* = 6.4 Hz, 1H), 6.16 (s, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.21 (d, *J* = 6.4 Hz, 2H), 3.15 (s, 2H), 3.07 - 3.04 (m, 2H), 3.02 - 2.97 (m, 1H), 2.91 - 2.85 (m, 1H), 2.27 - 2.09 (m, 8H), 2.07 - 1.97 (m, 2H), 1.87 - 1.81 (m, 2H), 1.78 - 1.73 (m, 2H), 1.65 (s, 1H), 1.62 (s, 6H), 1.59 - 1.46 (m, 3H), 1.35 - 1.26 (m, 1H), 1.13 - 0.97 (m, 2H)
I-58	ATH	BNS	805.4	12.54 (s, 1H), 11.09 (s, 1H), 9.36 (d, *J* = 1.2 Hz, 1H), 9.06 - 9.04 (m, 1H), 8.94 (d, *J* = 2.4 Hz, 1H), 8.80 (dd, *J* = 1.6, 2.4 Hz, 1H), 7.90 - 7.86 (m, 1H), 7.58 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.47 (t, *J* = 5.6 Hz, 1H), 6.38 - 6.17 (m, 1H), 5.05 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.56 - 3.35 (m, 2H), 3.20 (s, 2H), 3.11 (s, 2H), 3.06 - 2.97 (m, 1H), 2.94 - 2.83 (m, 1H), 2.63 - 2.53 (m, 1H), 2.48 - 2.45 (m, 1H), 2.27 (s, 2H), 2.23 (s, 1H), 2.20 - 2.09 (m, 4H), 2.06 - 2.00 (m, 1H), 1.84 (d, *J* = 11.2 Hz, 2H), 1.79 - 1.73 (m, 2H), 1.68 - 1.64 (m, 1H), 1.63 (s, 6H), 1.61 - 1.47 (m, 3H), 1.38 - 1.28 (m, 1H), 1.12 - 0.99 (m, 2H)
I-59	BNU	BAX	940.4	12.54 (s, 1H), 11.09 (s, 1H), 9.06 (s, 1H), 8.51 - 8.42 (m, 1H), 8.38 (t, *J* = 7.6 Hz, 1H), 8.23 - 8.16 (m, 1H), 7.88 (s, 1H), 7.61 - 7.55 (m, 1H), 7.03 (dd, *J* = 8.0, 14.2 Hz, 2H), 6.52 - 6.40 (m, 1H), 6.07 (s, 1H), 5.10 - 5.00 (m, 1H), 3.22 - 3.14 (m, 4H), 3.07 - 2.98 (m, 1H), 2.97 - 2.80 (m, 2H), 2.63 - 2.52 (m, 2H), 2.27 - 2.16 (m, 4H), 2.16 - 2.05 (m, 6H), 2.05 - 1.99 (m, 1H), 1.93 - 1.84 (m, 2H), 1.84 - 1.78 (m, 2H), 1.72 - 1.65 (m, 4H), 1.63 (s, 6H), 1.60 - 1.51 (m, 3H), 1.49 -1.40 (m, 4H), 1.11 - 0.95 (m, 2H)
I-60	ATH	BNJ	829.5	11.08 (s, 1H), 8.25 (s, 1H), 8.21 - 8.16 (m, 1H), 7.94 - 7.89 (m, 2H), 7.61 - 7.49 (m, 2H), 7.41 - 7.34 (m, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.47 (m, 1H),

				5.19 - 5.10 (m, 1H), 5.04 (dd, *J* = 5.4, 12.8 Hz, 1H), 4.07 - 3.95 (m, 1H), 3.75 - 3.67 (m, 1H), 3.24 - 3.11 (m, 4H), 3.07 - 2.95 (m, 4H), 2.93 - 2.81 (m, 1H), 2.61 - 2.53 (m, 1H), 2.28 - 2.09 (m, 7H), 2.06 - 1.96 (m, 1H), 1.89 - 1.80 (m, 2H), 1.74 (m, 2H), 1.67 - 1.56 (m, 3H), 1.56 - 1.45 (m, 8H), 1.40 - 1.25 (m, 2H), 1.12 - 0.97 (m, 2H)
I-61	ATH	BNO	941.6	11.10 (s, 1H), 10.74 - 10.55 (m, 1H), 8.76 (d, *J* = 7.6 Hz, 1H), 8.29 - 8.20 (m, 2H), 7.90 - 7.83 (m, 1H), 7.64 - 7.53 (m, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.87 - 6.36 (m, 2H), 5.80 - 4.99 (m, 3H), 4.77 - 4.63 (m, 1H), 3.84 - 3.69 (m, 3H), 3.20 (s, 3H), 3.13 - 2.97 (m, 4H), 2.94 - 2.84 (m, 2H), 2.64 - 2.52 (m, 2H), 2.29 - 2.24 (m, 2H), 2.23 - 2.17 (m, 2H), 2.17 - 2.12 (m, 2H), 2.11 - 2.00 (m, 2H), 2.00 - 1.88 (m, 2H), 1.85 (d, *J* = 10.0 Hz, 2H), 1.80 - 1.73 (m, 2H), 1.68 - 1.62 (m, 3H), 1.57 (s, 6H), 1.55 - 1.47 (m, 2H), 1.47 - 1.14 (m, 2H), 1.13 - 0.99 (m, 2H)

For Method 2, when the amine is the HCl salt, TEA was added to free base the salt, followed by HOAc to adjust the pH to 3-4 or 5-7. KOAc could also be used in place of the TEA/HOAc combination. Method 2 was run anywhere from 0.5-48 hrs and the reaction temperature was run from -15 °C to rt. The final products were isolated under standard purification techniques including reverse HPLC, silica gel chromatography, and prep-TLC with appropriate solvent conditions. [a] The ^{1}H NMR was measured using $CDCl_3$ as the solvent.

Example 3. IRAK4 MSD Degradation in OCI-LY10

[001134] Degradation of IRAK4 in OCI-LY10 was quantitatively measured using Meso Scale Discovery technology. OCI-LY10 cells were seeded in 96-well plates (Corning 3799) with a density of 300,000 cells per well in 100 µL fresh media. Compounds were then added to the assay plates with a final top concentration of 1 to 10 µM in a 1:3 dilution series with total of 8 doses. The assay plates were then incubated for 4 to 24 hours at 37 °C under 5% CO2. The assay plates were then centrifuged for 5 minutes and the cell pellets were treated with 100 µL/well RIPA lysis buffer (Boston BioProducts BP-115D) with proteinase inhibitors. To prepare MSD assay plates (Meso Scale Discovery Catalog number L15XA-3), the plates were coated with 2µg/mL capture antibody (mouse Anti-IRAK4 antibody [2H9], ab119942) in PBS, at 40 µL/well. The plates were then incubated overnight at 4 °C, washed 3 times with 150 µL/well TBST buffer (Cell Signaling Technology, Catalog number 9997S) and blocked with 150 µL/well blocking buffer (Meso Scale Discovery Catalog number R93BA-4). Cell lysates were then added to MSD assay plates and the plates were incubated at room temperature for 1 hour. The plates were then washed 3 times with 150 µL/well TBST buffer and 25µL/well primary detection antibody (rabbit Anti-IRAK4 antibody [Y279], from Abcam. Catalog number ab32511, 1 µg/mL). The assay plates were then incubated at room temperature for 1 hour, washed 3 times with 150 µL/well TBST buffer and 25µL/well secondary detection antibody,

SULFO-TAG anti-rabbit antibody were added (anti rabbit antibody from Meso Scale Discovery, Catalog number R32AB-1, 1 μg/mL). The assay plates were then incubated at room temperature for 1 hour, washed 3 times with 150 μL/well TBST buffer, and 150 μL/well MSD reading buffer (Meso Scale Discovery catalog number R92TC-2) was added. The plates were then analyzed by a MSD reader (Meso Scale Discovery, Model Quick Plex SQ 120). The data was then analyzed by software Prism 7.0 from GraphPad and the dose-depended IRAK4 degradation were fit using a three-parameter logistic equation to calculate DC_{50}.

[001135] IRAK4 MSD degradation results in OCI-LY10 cells for compounds of the invention are presented in **Table 5**. The letter codes for IRAK4 DC_{50} include: A (<0.05 μM); B (0.05 – 0.1 μM); C (0.1 – 0.5 μM); D (0.5 – 1.0 μM); and E (>1.0 μM).

Table 5. IRAK4 MSD Degradation in OCI-LY10 Results

I-#	IRAK4 degradation in OCI-LY10 at 4 hrs: DC_{50} (μM)	IRAK4 degradation in OCI-LY10 at 24 hrs: DC_{50} (μM)
I-3	B	A
I-19	-	B
I-20	-	B
I-21	-	C
I-22	-	B
I-23	-	A
I-24	-	A
I-25	-	B
I-26	-	A
I-27	-	A
I-28	-	A
I-29	-	A
I-30	-	A
I-31	-	A
I-32	-	A
I-33	-	A
I-34	-	A
I-35	-	B
I-40	-	C
I-41	-	A
I-42	-	B
I-45	-	A
I-46	-	B
I-47	-	A
I-48	-	E
I-49	-	E
I-50	-	D
I-51	-	E
I-53	-	C
I-54	-	C
I-55	-	E
I-56	-	A
I-59	-	C
I-60	-	A
I-61	-	E
I-62	-	B
I-63	-	A
I-65	-	A
I-66	-	A

Example 4. Cell viability Assay with OCI-LY10 and SUDHL-2

[001136] Compound-mediated viability effect on OCI-LY10 or SUDHL-2 was quantitatively determined using the CellTiter-Glo® Luminescent Cell Viability Assay kit from Promega (Catalog number G7570) following manufacturer's recommended procedures. Briefly, OCI-LY10 or SUDHL-2 cells were seeded into 384 well plates (Grenier Bio-One, Catalog number 781080) with a density of 10,000 cells per well. Compounds were then added to the assay plate with final top concentration of 10μM and 1:3 dilution series with total of 9 doses. The final DMSO concentration was normalized to 0.2%. The assay plates were incubated at 37 °C for 4 days under 5% CO_2. Then the assay plate was equilibrated at room temperature for 10 minutes. To determine cell viability, 30 μL CellTiter Glo reagent was added to each well and the assay plate was centrifuged at 1000 rpm for 30 second, incubated at room temperature for 10 min, and analyzed by detecting the luminescence using a multimode plate reader (EnVision 2105, PerkinElmer). The data was then analyzed by software Prism 7.0 from GraphPad and the dose response curves were fit using a three-parameter logistic equation to calculate IC_{50}.

[001137] CTG Cell Viability Assay – OCI-LY10 and SUDHL-2 results for compounds of the invention are presented in **Table 6**. The letter codes for IRAK4 IC_{50} include: A (<0.05 μM); B (0.05 – 0.1 μM); C (0.1 – 0.5 μM); D (0.5 – 1.0 μM); and E (>1.0 μM).

Table 6. CTG Cell Viability Assay Results

I-#	CTG Cell Viability Assay - OCI-LY10: IC_{50} (μM)	CTG Cell Viability Assay - SUDHL-2: IC_{50} (μM)
I-3	A	-
I-19	C	-
I-20	A	-
I-21	C	-
I-22	A	-
I-23	C	-
I-24	A	-
I-25	A	-
I-26	B	-
I-27	A	-
I-28	C	-
I-29	A	-
I-30	B	-
I-31	A	-
I-32	B	-
I-33	A	-
I-34	B	-
I-35	D	-
I-40	A	-
I-41	A	-
I-42	A	-
I-45	C	-
I-46	A	-
I-47	A	-
I-48	B	-
I-49	B	-
I-50	A	-
I-51	A	-
I-53	A	-
I-54	A	-
I-55	A	-

I-57	A	-
I-58	A	-
I-59	C	-
I-60	A	-

I-63	A	-
I-64	A	-
I-65	A	-
I-66	A	-

Example 5: Quantification of Ikaros and Aiolos Degradation.

[001138] Degradation of Ikaros (protein product of gene IKZF1) and Aiolos (protein product of gene IKZF3) were determined by quantitative immunoblotting as follows. OCI-LY10 cells, $2x10^6$ cells/well, were treated with listed concentrations of IRAK4 degraders or control compounds in 6 well plates for 6 h. Cells were collected, washed with cold PBS, lysed in RIPA buffer (Boston BioProducts BP-115D) with protease / phosphatase inhibitor cocktail (Roche 05892791001 / Roche 04906837001) and centrifuged at 13000 RPM for 20 min to precipitate insoluble material. The supernatant fraction was diluted in SDS-PAGE loading buffer (Beyotime Bio P0015) and 20 μL of each sample was resolved on 4-12% Bis-Tris SDS-PAGE gels (Novex, WG1402BOX). Resolved samples were transferred to nitrocellulose membranes by wet electro-transfer method at 250 mV for 1.5 h. The membrane was blocked with LICOR blocking buffer (LI-COR, 927-50000) for 1 hour, washed three times with TBST (CST#9997S) for 5 minutes each and incubated with primary antibody prepared in block buffer with 0.1% Tween-20 (Solarbio, P8220) at 4 °C overnight. Ikaros antibody was rabbit monoclonal D6N9Y (CST#14859), at 1:1000 dilution. Aiolos antibody was rabbit monoclonal D1C1E (CST#15103), at 1:1000 dilution. Signal was normalized to mouse anti-beta-Actin monoclonal 8H10D10 (CST#3700) used at 1:10,000 dilution. After incubation in primary antibodies, membranes were washed three times with TBST, 5 minutes each, incubated with fluorescently labeled secondary antibodies anti-rabbit IgG (Licor,926-32211) at 1:5000 dilution; anti-mouse IgG (LI-COR, 926-68070) at 1:5000 dilution, for 1 hour at RT. After incubation in secondary, membranes were washed three times with TBST, 5 minutes each and read on LICOR Odyssey imager. Data was reported as signal for Ikaros or Aiolos relative to signal for actin, and normalized to DMSO-treated control.

[001139] Ikaros and Aiolos degradation assay results in OCI-LY10 cells for compounds of the invention are presented in **Table 7**. The letter codes for Ikaros and Aiolos DC_{50} include: A (<0.05 μM); B (0.05 – 0.1 μM); C (0.1 – 0.5 μM); D (0.5 – 1.0 μM); and E (>1.0 μM).

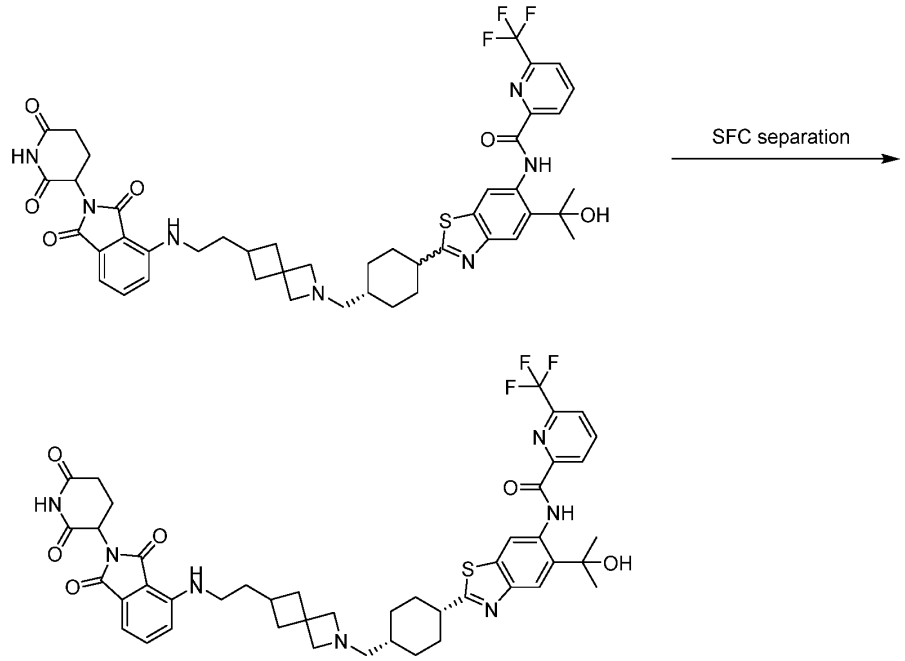
Table 7. Ikaros and Aiolos Degradation Assay Results

I-#	Ikaros Degradation in OCI-LY10: DC_{50} (μM)	Aiolos Degradation in OCI-LY10: DC_{50} (μM)
I-3	A	A
I-4	A	A
I-5	A	A

I-7	A	A
I-8	A	A
I-9	B	A
I-10	A	A
I-11	C	B
I-12	A	A
I-13	A	A
I-14	B	A
I-15	C	B
I-16	A	-
I-17	A	A
I-18	A	A
I-19	B	A
I-20	C	C
I-21	B	A
I-22	A	A
I-23	C	A
I-24	A	A
I-25	A	A
I-26	A	A
I-27	A	A
I-28	B	A
I-29	A	A
I-30	A	A
I-31	A	A
I-32	A	A

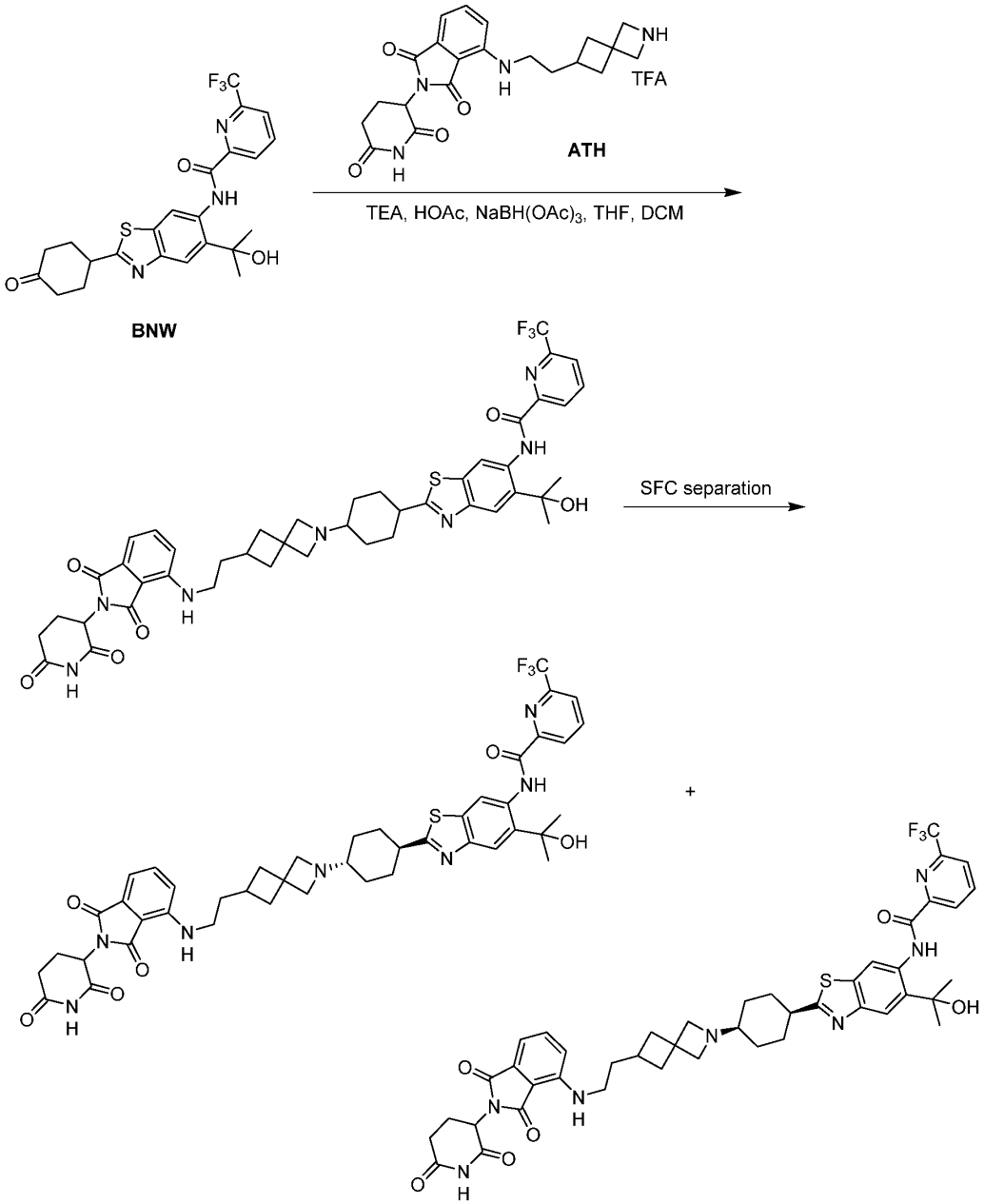
I-33	A	A
I-34	A	A
I-35	A	A
I-36	A	A
I-38	A	A
I-39	A	A
I-40	A	A
I-41	A	A
I-42	A	A
I-43	A	A
I-44	A	A
I-45	C	C
I-46	A	A
I-47	A	A
I-48	A	A
I-49	A	A
I-50	A	A
I-53	A	A
I-54	A	A
I-55	A	A
I-56	A	A
I-59	C	C
I-62	A	A
I-63	A	A
I-65	A	A
I-66	A	A

Example 6. Synthesis of N-(2-((1S,4S)-4-((6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino) ethyl)-2-azaspiro[3.3]heptan-2-yl)methyl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide (I-62)



[001140] One synthesis of N-[2-[4-[[6-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]-2-azaspiro[3.3]heptan-2-yl]methyl]cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (600 mg, 688 umol, Example I-3), led to 10-15% of cis-isomer being formed. This batch was separated by SFC (column: DAICEL CHIRALPAK IE (250mm*30 mm,10 um); mobile phase [IPA+25%ACN (0.1%IPAM)]) to give two isomers. The first fraction, ((1S,4S)-4-((6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)ethyl)-2-azaspiro[3.3]heptan-2-yl)methyl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide (120 mg, 20% yield), was obtained as yellow solid. The crude product was further purified by Prep-HPLC (column: Phenomenex luna C18 150*25mm * 10um; mobile phase: [water (0.225%FA)-ACN]) to give N-(2-((1S,4S)-4-((6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino) ethyl)-2-azaspiro[3.3]heptan-2-yl)methyl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide (62.1 mg, 51% yield, FA salt, tR = 2.74, 4.64) as yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ 12.55 (s, 1H), 11.09 (s, 1H), 9.06 (s, 1H), 8.51 - 8.42 (m, 1H), 8.38 (t, J = 8.0 Hz, 1H), 8.19 (dd, J = 0.8, 7.6 Hz, 1H), 7.89 (s, 1H), 7.57 (dd, J = 7.2, 8.4 Hz, 1H), 7.11 - 6.97 (m, 2H), 6.46 (t, J = 5.6 Hz, 1H), 6.26 - 5.90 (m, 1H), 5.05 (dd, J = 5.4, 12.8 Hz, 1H), 3.33 (s, 2H), 3.29 - 3.13 (m, 5H), 2.94 - 2.82 (m, 1H), 2.62 - 2.52 (m, 2H), 2.42 (d, J = 6.0 Hz, 2H), 2.27 - 2.10 (m, 3H), 2.09 - 1.94 (m, 3H), 1.93 - 1.71 (m, 4H), 1.69 - 1.49 (m, 11H), 1.43 - 1.32 (m, 2H); LC-MS (ESI+) m/z 872.5 $(M+H)^+$.

Example 7. Syntheses of N-(2-((1R,4R)-4-(6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl) -2-azaspiro[3.3]heptan-2-yl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide (I-63) and N-(2-((1S,4S)-4-(6-(2-((2-(2,6-dioxopiperidin-3-yl) -1,3-dioxoisoindolin-4-yl)amino)ethyl)-2-azaspiro[3.3]heptan-2-yl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide (I-64)



[001141] Step 1 - N-(2-(4-(6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-2 -azaspiro[3.3]heptan-2-yl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide

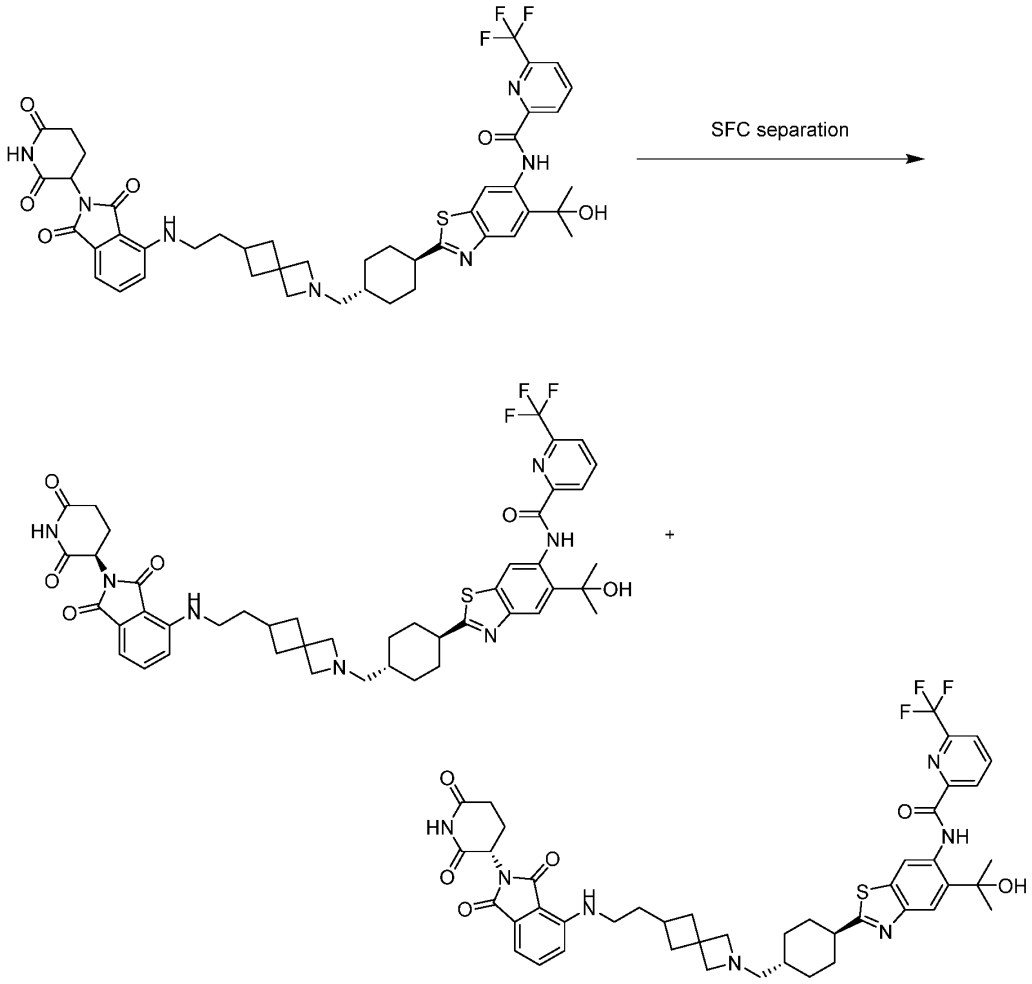
[001142] To a solution of N-[5-(1-hydroxy-1-methyl-ethyl)-2-(4-oxocyclohexyl)-1,3-benzothiazol-6-yl]-6- (trifluoromethyl)pyridine-2-carboxamide (240 mg, 503 umol, Intermediate BNW) and 4-[2-(2-azaspiro[3.3]heptan-6-yl) ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (308 mg, 603 umol, TFA, Intermediate ATH) in the THF (3 mL) and DCM (3 mL) was added TEA (50.9 mg, 503 umol) at 40 °C. The mixture was stirred at 40 °C for 5 mins. Then HOAc (30.2 mg, 503 umol) was added and the mixture was stirred at 40 °C for 25 mins. Next, $NaBH(OAc)_3$ (160 mg, 754 umol) was added and the mixture was stirred at 40 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um;mobile phase: [water (0.225%FA)-ACN]; B%: 30%-60%,8.5min) to give the title compound (320 mg, 67% yield, FA salt) as yellow solid. LC-MS (ESI^+) m/z 858.4 $(M+H)^+$.

[001143] Step 2 - N-(2-((1r,4r)-4-(6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl) -2-azaspiro[3.3]heptan-2-yl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide and N-(2-((1s,4s)-4-(6-(2-((2-(2,6-dioxopiperidin-3-yl) -1,3-dioxoisoindolin-4-yl)amino)ethyl)-2-azaspiro[3.3]heptan-2-yl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide

[001144] The racemic N-[2-[4-[6-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]-2- azaspiro[3.3]heptan-2-yl]cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (320 mg, 373 umol) was separated by SFC (column: DAICEL CHIRALPAK IC (250mm*50mm,10um); mobile phase: [0.1%NH_3H_2O IPA]; B%: 60%-60%, 7.5min; 150minmin) to give two fractions. The first peak was re-purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10 um; mobile phase: [water(0.225% FA)-ACN]; B%: 30%-60%, 8.5 min) to give N-(2-((1S,4S)-4-(6-(2-((2-(2,6-dioxopiperidin-3-yl) -1,3-dioxoisoindolin-4-yl)amino)ethyl)-2-azaspiro[3.3]heptan-2-yl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide (93.0 mg, 28%, FA salt) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 11.09 (s, 1H), 9.07 (s, 1H), 8.50 - 8.44 (m, 1H), 8.39 (t, J = 7.6 Hz, 1H), 8.20 - 8.18 (m, 1H), 7.90 (s, 1H), 7.58 (dd, J = 7.2, 8.4 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 6.48 (t, J = 6.0 Hz, 1H), 6.08 (s, 1H), 5.05 (dd, J = 5.4, 12.8 Hz, 1H), 3.24 - 3.17 (m, 5H), 3.11 (d, J = 1.2 Hz, 2H), 2.93 - 2.83 (m, 1H), 2.58 (d, J = 17.6 Hz, 1H), 2.55 - 2.52 (m, 1H), 2.32 - 2.32 (m, 1H), 2.32 - 2.25 (m, 1H), 2.24 - 2.19 (m, 2H), 2.18 - 2.11 (m, 1H), 2.08 - 1.95 (m, 3H), 1.82 - 1.73 (m, 4H), 1.70 - 1.64 (m, 2H), 1.64 (s, 6H), 1.52 (d, J = 4.0 Hz, 4H). LC-MS (ESI^+) m/z 858.1 $(M+H)^+$. The second peak was re-purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um;mobile phase: [water (10mM NH_4HCO_3)-

ACN];B%: 48%-78%, 11.5 min) to give N-(2-((1R,4R)-4-(6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl) -2-azaspiro[3.3]heptan-2-yl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide (53 mg, 17%, free base) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 11.08 (br s, 1H), 9.06 (s, 1H), 8.49 - 8.44 (m, 1H), 8.39 (t, J = 7.6 Hz, 1H), 8.22 - 8.16 (m, 1H), 7.89 (s, 1H), 7.59 (dd, J = 7.2, 8.4 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.48 (t, J = 5.6 Hz, 1H), 6.14 - 6.01 (m, 1H), 5.06 (dd, J = 5.2, 12.8 Hz, 1H), 3.22 (q, J = 6.4 Hz, 2H), 3.11 (s, 2H), 3.00 (s, 3H), 2.94 - 2.84 (m, 1H), 2.63 - 2.57 (m, 1H), 2.56 - 2.52 (m, 1H), 2.23 - 2.17 (m, 3H), 2.16 - 2.10 (m, 2H), 2.07 - 2.00 (m, 1H), 1.96 - 1.89 (m, 1H), 1.83 - 1.73 (m, 4H), 1.70 - 1.65 (m, 2H), 1.63 (s, 6H), 1.59 - 1.50 (m, 2H), 1.11 - 1.02 (m, 2H); LC-MS (ESI$^+$) m/z 858.1 $(M+H)^+$. The cis and trans isomers were assigned arbitrarily.

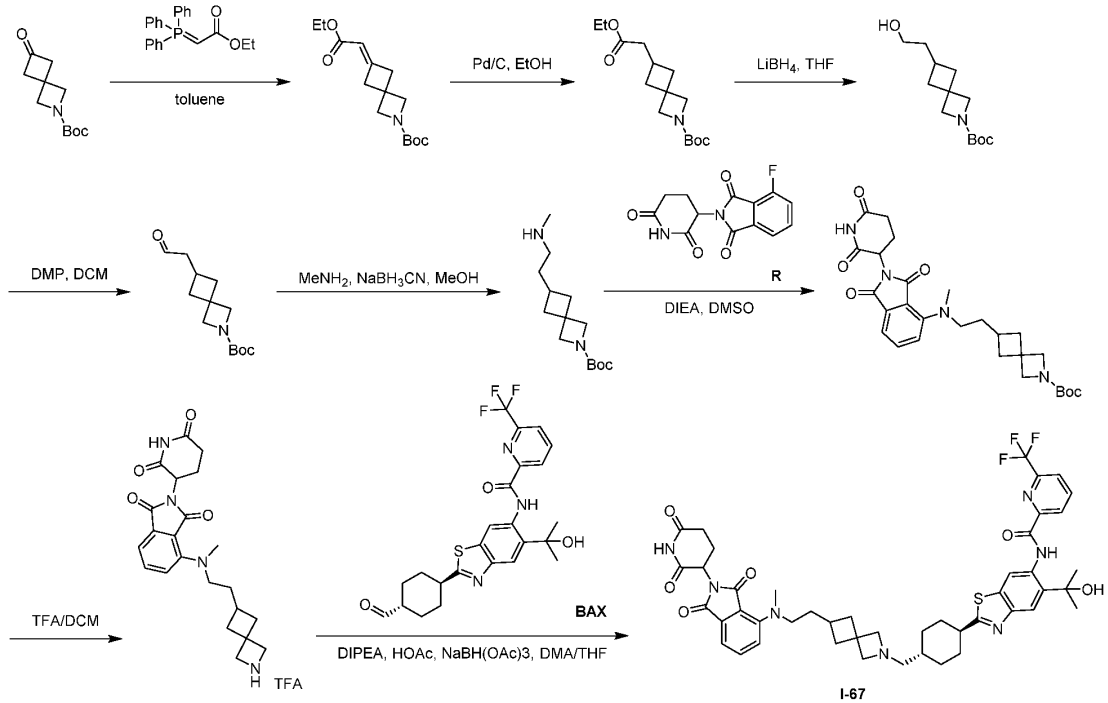
Example 8. Syntheses of N-[2-[4-[[6-[2-[[2-[(3R)-2,6-dioxo-3-piperidyl]-1,3-dioxo-isoindolin-4-yl]amino]ethyl]- 2-azaspiro[3.3]heptan-2-yl]methyl]cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (I-65) and N-[2-[4-[[6-[2-[[2-[(3S)-2,6-dioxo-3-piperidyl]-1,3 -dioxo-isoindolin-4-yl]amino]ethyl]-2-azaspiro[3.3]heptan-2-yl]methyl]cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (I-66)



[001145] N-[2-[4-[[6-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]ethyl]-2-azaspiro[3.3]heptan-2-yl]methyl]cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (600 mg, 688 umol, Example I-3) was separated by SFC. The reactant was separated by SFC (column: DAICEL CHIRALPAK IA (250mm*30mm, 10um); mobile phase: [0.1%NH_3H_2OIPA]; B%: 50%-50% 9.5 min; 200 min) to give the impure peak 1 and peak 2. The impure peak 1 and peak 2 was purified by reverse phase (0.1% FA) to give N-[2-[4-[[6-[2-[[2-[(3R)-2,6-dioxo-3-piperidyl]-1,3-dioxo-isoindolin-4-yl]amino]ethyl]- 2-azaspiro[3.3]heptan-2-yl]methyl]cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (204 mg, 64% yield, 99% purity, FA salt) as yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 11.09 (s, 1H), 9.06 (s, 1H), 8.49 - 8.44 (m, 1H), 8.38 (t, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.88 (s, 1H), 7.62 - 7.54 (m, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 6.47 (t, J = 5.6 Hz, 1H), 6.22 - 5.96 (m, 1H), 5.08 - 5.02 (m, 1H), 3.25 (s, 2H), 3.21 (d, J = 6.0 Hz, 2H), 3.15 (s, 2H), 3.05 - 2.98 (m, 1H), 2.94 -

2.82 (m, 1H), 2.63 - 2.51 (m, 3H), 2.34 - 2.29 (m, 2H), 2.24 - 2.11 (m, 5H), 2.07 - 1.98 (m, 1H), 1.89 - 1.80 (m, 2H), 1.80 - 1.72 (m, 2H), 1.65 (s, 1H), 1.63 (s, 6H), 1.58 - 1.47 (m, 2H), 1.40 - 1.27 (m, 1H), 1.13 - 0.98 (m, 2H); LC-MS (ESI$^+$) *m/z* 872.6 (M+H)$^+$; and N-[2-[4-[[6-[2-[[2-[(3S)-2,6-dioxo-3-piperidyl]-1,3 -dioxo-isoindolin-4-yl]amino]ethyl]-2-azaspiro[3.3]heptan-2-yl]methyl]cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (233mg, 73% yield, 99% purity, FA salt) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 11.20 - 10.94 (m, 1H), 9.06 (s, 1H), 8.50 - 8.44 (m, 1H), 8.38 (t, *J* = 7.6 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.63 - 7.55 (m, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.47 (t, *J* = 6.0 Hz, 1H), 6.16 - 5.99 (m, 1H), 5.09 - 5.01 (m, 1H), 3.27 (s, 2H), 3.21 (d, *J* = 6.8 Hz, 2H), 3.17 (s, 2H), 3.05 - 2.98 (m, 1H), 2.94 - 2.83 (m, 1H), 2.64 - 2.51 (m, 3H), 2.32 (d, *J* = 6.4 Hz, 2H), 2.25 - 2.10 (m, 5H), 2.06 - 1.98 (m, 1H), 1.84 (d, *J* = 11.6 Hz, 2H), 1.80 - 1.73 (m, 2H), 1.68 - 1.64 (m, 1H), 1.63 (s, 6H), 1.58 - 1.46 (m, 2H), 1.43 - 1.28 (m, 1H), 1.13 - 1.00 (m, 2H); LC-MS (ESI$^+$) *m/z* 872.6 (M+H)$^+$. The absolute configuration of the stereoisomers was assigned arbitrarily.

Example 9. Synthesis of N-[5-(2-hydroxypropan-2-yl)-2-[(1r,4r)-4-{[6-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl](methyl)amino}ethyl)-2-azaspiro[3.3]heptan-2-yl]methyl}cyclohexyl]-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (I-67)



[001146] Step 1 - Tert-butyl 6-(2-ethoxy-2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate

[001147] A mixture of ethyl 2-(triphenylphosphoranylidene)acetate (3.63 g, 10.4 mmol, CAS#1099-45-2) and tert-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (2.00 g, 9.47 mmol, CAS#1147557-97-8) in toluene (30 mL) was stirred at 80 °C for 4 hours. On completion, the mixture was concentrated in vacuum. The residue was purified by column chromatography (SiO_2, PE: EtOAc= 1:0 to 3: 1) to give the title compound (2.50 g, 90% yield) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 5.64 (t, J = 2.4 Hz, 1 H), 4.13 (q, 2 H), 4.01 - 3.92 (m, 4 H), 3.28 (s, 2 H), 3.00 (s, 2 H), 1.43 (s, 9 H), 1.50 (t, J = 6.8 Hz, 3 H).

[001148] Step 2 - Tert-butyl 6-(2-ethoxy-2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate

[001149] To a solution of tert-butyl 6-(2-ethoxy-2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate (2.50 g, 8.89 mmol) in EtOH (30 mL) and was added Pd/C (250 mg, 10% wt on active carbon) under N_2. The suspension was degassed in vacuum and purged with H_2 several times. The mixture was stirred at 25 °C for 12 hours under H_2 (25 Psi). On completion, the reaction mixture was filtered and the filter cake was dried in vacuum to give the title compound (2.50 g, 99% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (q, J = 7.2 Hz, 2 H), 3.92 (s, 2 H), 3.79 (s, 2 H), 2.54- 2.47 (m, 1 H), 2.38 - 2.30 (m, 4 H), 1.89 - 1.81 (m, 2 H), 1.41 (s, 9 H), 1.23 (t, J = 7.2 Hz, 3 H). LC-MS (ESI$^+$) m/z 228.0 $(M-56+H)^+$.

[001150] Step 3 - Tert-butyl 6-(2-hydroxyethyl)-2-azaspiro[3.3]heptane-2-carboxylate

[001151] To a solution of tert-butyl 6-(2-ethoxy-2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate (1.90 g, 6.71 mmol) and in THF (20 mL) was added $LiBH_4$ (321 mg, 14.8 mmol) slowly at 0 °C under N_2. The mixture was stirred at 25 °C for 2 hours. On completion, the mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give the title compound (800 mg, 64.0%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 2 H), 3.80 (s, 2 H), 3.58 (t, J = 6.8 Hz, 2 H), 2.33 - 2.23 (m, 3 H), 1.86 - 1.76 (m, 2 H), 1.67 - 1.61 (m, 2 H), 1.43 (s, 9 H).

[001152] Step 4 - Tert-butyl 6-(2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate

[001153] To a solution of tert-butyl 6-(2-hydroxyethyl)-2-azaspiro[3.3]heptane-2-carboxylate (850 mg, 3.52 mmol) in DCM (20 mL) was added DMP (1.94 g, 4.58 mmol) at 25 °C under N_2. The mixture was stirred at 25 °C for 2 hours. On completion, the residue was quenched with $Na_2S_2O_3$ aqueous solution (15 mL). The aqueous phase was extracted with ethyl acetate (2 X 25 mL). The combined organic phases were washed with brine (15 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, PE: EtOAc= 1:0 to 1: 1) to give the title compound (800 mg, 95% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1 H), 3.94 (s, 2 H), 3.81 (s, 2 H), 2.63 - 2.50 (m, 3 H), 2.43 - 2.34 (m, 2 H), 1.92 - 1.79 (m, 2 H), 1.42 (s, 9 H).

[001154] Step 5 - Tert-butyl 6-(2-(methylamino)ethyl)-2-azaspiro[3.3]heptane-2-carboxylate

[001155] To a mixture of tert-butyl 6-(2-oxoethyl)-2-azaspiro[3.3]heptane-2-carboxylate (800 mg,

3.34 mmol) and methanamine;hydrochloride (2.26 g, 33.4 mmol) in MeOH (20 mL) was added $NaBH_3CN$ (1.05 g, 16.7 mmol) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 hours. On completion, the residue was added water (20 mL). The aqueous phase was extracted with ethyl acetate (3 x 40 mL). The combined organic phases were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give the title compound (730 mg, 85% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 3.99 - 3.92 (m, 2 H), 3.87 (s, 2 H), 2.97 - 2.78 (m, 2 H), 2.70 (s, 3 H), 2.42 - 2.35 (m, 2 H), 2.29 - 2.16 (m, 1 H), 1.95 - 1.79 (m, 4 H), 1.42 (s, 9 H).

[001156] Step 6 - Tert-butyl 6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)(methyl)amino)ethyl)-2-azaspiro[3.3]heptane-2-carboxylate

[001157] To a mixture of tert-butyl 6-(2-(methylamino)ethyl)-2-azaspiro[3.3]heptane-2-carboxylate (331 mg, 1.30 mmol) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (300 mg, 1.09 mmol, CAS#835616-60-9) in DMSO (10 mL) was added DIEA (281 mg, 2.17 mmol) in one portion at 25 °C under N_2. The mixture was stirred at 100 °C for 1 hour. On completion, the mixture was added water (5 mL) and stirred for 5 minutes. The aqueous phase was extracted with ethyl acetate (2 x 15 mL). The combined organic phases were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, PE: EtOAc = 1:0 to 1: 1) to give the title compound (300 mg, 54% yield) as a yellow solid. LC-MS (ESI^+) m/z 511.1 $(M+H)^+$.

[001158] Step 7 - 4-((2-(2-Azaspiro[3.3]heptan-6-yl)ethyl)(methyl)amino)-2-(2,6-dioxopiperidin-3-yl) isoindoline-1,3-dione

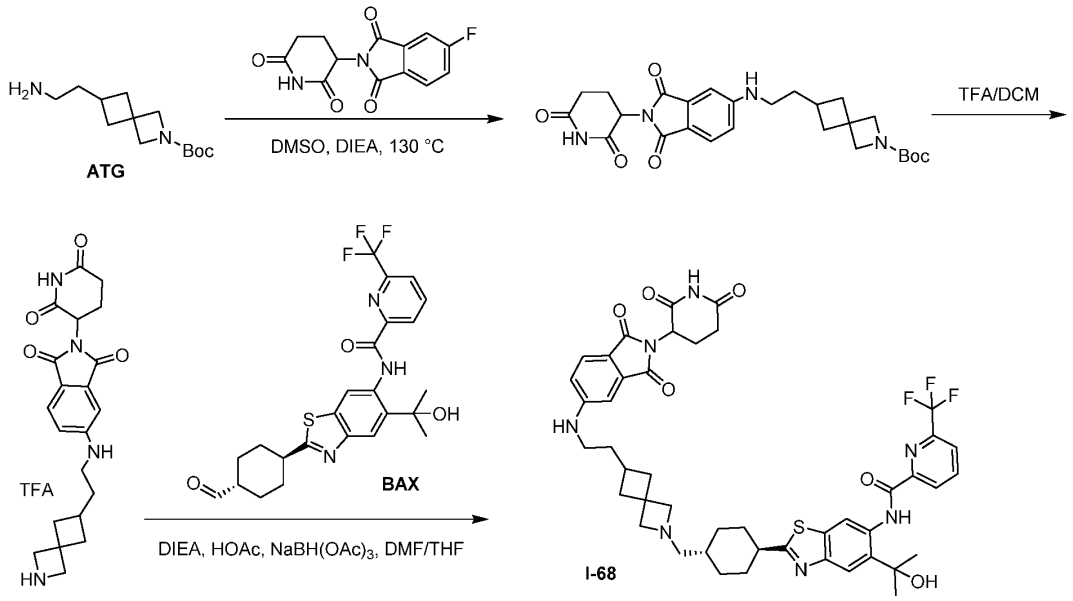
[001159] To a solution of tert-butyl 6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)(methyl)amino) ethyl)-2-azaspiro[3.3]heptane-2-carboxylate (80.0 mg, 157 μmol) in DCM (3 mL) was added TFA (715 mg, 6.27 mmol) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 1 hour. On completion, the mixture was concentrated in vacuum to give the title compound (55.0 mg, 100% yield, TFA salt) as a yellow solid. LC-MS (ESI^+) m/z 411.1 $(M+H)^+$.

[001160] Step 8 - N-(2-((1r,4r)-4-((6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)(methyl)amino) ethyl)-2-azaspiro[3.3]heptan-2-yl)methyl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide (**I-67**)

[001161] To a solution of 4-((2-(2-azaspiro[3.3]heptan-6-yl)ethyl)(methyl)amino)-2-(2,6-dioxopiperidin-3-yl) isoindoline-1,3-dione (55.5 mg, 106 μmol, TFA) in DMA (0.4 mL) and THF (2 mL) was added DIEA (21.0 mg, 163 μmol) at -20 °C. Then *N*-(2-((1r,4r)-4-formylcyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide (40.0 mg, 81.4 μmol) and HOAc (9.8 mg, 163 umol) was added to the above mixture, and the resulting mixture was stirred at -20 °C for 0.5 hour. Then $NaBH(OAc)_3$ (86.2 mg, 407 μmol) was added to the mixture and the mixture was stirred at -20 °C for 1.5 hours. On completion, the mixture was concentrated in vacuum. The residue was purified

by prep-HPLC (FA condition, column: Phenomenex luna C18, 150mm*25mm*10μm; mobile phase: [water (0.225%FA)-MeCN]; B%: 27%-57%, 10 min) to give the title compound (15.0 mg, 20% yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.55 (s, 1 H), 11.09 (s, 1 H), 9.07 (s, 1 H), 8.47 (d, J = 8.0 Hz, 1 H), 8.39 (t, J = 8.0 Hz, 1 H), 8.24 - 8.16 (m, 1 H), 7.89 (s, 1 H), 7.67 - 7.61 (m, 1 H), 7.28 - 7.22 (m, 2 H), 6.08 (s, 1 H), 5.13 - 5.04 (m, 1 H), 3.71 - 3.47 (m, 3 H), 3.45 - 3.37 (m, 3 H), 3.09 - 3.03 (m, 1 H), 2.99 (s, 3 H), 2.95 - 2.84 (m, 1 H), 2.66 - 2.53 (m, 3 H), 2.24 - 2.12 (m, 4 H), 2.11 - 1.92 (m, 2 H), 1.88 - 1.73 (m, 4 H), 1.64 (s, 9 H), 1.60 - 1.52 (m, 2 H), 1.52 - 1.40 (m, 1 H), 1.20 - 1.02 (m, 2 H). LC-MS (ESI$^+$) m/z 886.4 $(M+H)^+$.

Example 10. Synthesis of N-[5-(2-hydroxypropan-2-yl)-2-[(1r,4r)-4-{[6-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino}ethyl)-2-azaspiro[3.3]heptan-2-yl]methyl}cyclohexyl]-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (I-68)



[001162] Step 1 - Tert-butyl 6-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]amino]ethyl]-2-azaspiro [3.3]heptane-2-carboxylate

[001163] To a solution of tert-butyl 6-(2-aminoethyl)-2-azaspiro[3.3]heptane-2-carboxylate (140 mg, 582 umol) in DMSO (3 mL) was added 2-(2,6-dioxo-3-piperidyl)-5-fluoro-isoindoline-1,3-dione (193 mg, 699 umol, prepared similarily to Intermediate R) and DIEA (225 mg, 1.75 mmol). The mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 130 °C for 3 hrs under N_2 atmosphere. On completion, the mixture was filtered and the filtrate was concentrated under reduced pressure to afford a residue. The residue was purified by reversed-phase HPLC (0.1% FA condition) to give

the title compound (40.0 mg, 14% yield) as a green solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.97 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 6.97 (s, 1H), 6.75 (d, J = 8.4 Hz, 1H), 4.94 (dd, J = 5.6, 12.4 Hz, 1H), 3.95 (s, 2H), 3.82 (s, 2H), 3.16 (t, J = 7.2 Hz, 2H), 2.93 - 2.87 (m, 1H), 2.85 - 2.72 (m, 2H), 2.37 - 2.31 (m, 2H), 2.28 - 2.19 (m, 1H), 2.16 - 2.10 (m, 1H), 1.87 - 1.82 (m, 2H), 1.77 - 1.70 (m, 2H), 1.44 (s, 9H).

[001164] Step 2 - 5-[2-(2-Azaspiro[3.3]heptan-6-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione

[001165] To a solution of tert-butyl 6-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]amino]ethyl]-2- azaspiro[3.3]heptane-2-carboxylate (40.0 mg, 80.5 umol) in DCM (2 mL) was added TFA (770 mg, 6.75 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was concentrated under reduced pressure to give the title compound (40.0 mg, 97% yield, TFA salt) as yellow oil. LC-MS (ESI$^+$) m/z 397.2 (M+H)$^+$.

[001166] Step 3 - N-[2-[4-[[6-[2-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]amino]ethyl]-2-azaspiro [3.3]heptan-2-yl]methyl]cyclohexyl]-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide **(I-68)**

[001167] To a mixture of 5-[2-(2-azaspiro[3.3]heptan-6-yl)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline- 1,3-dione (40.0 mg, 78.3 umol, TFA salt) in a mixed solvent of THF (5 mL) and DMF (1 mL) was added DIEA (20.2 mg, 156 umol) at -15 °C until pH = 8. The mixture was stirred at -15 °C for 10 mins, then HOAc (14.1 mg, 235 umol) was added at -15 °C until pH = 6. The mixture was stirred at -15 °C for 20 mins. Subsequently, N-[2-(4-formylcyclohexyl)-5-(1-hydroxy-1-methyl-ethyl)-1,3-benzothiazol -6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (38.5 mg, 78.3 umol) was added and the mixture was stirred at -15 °C for 1 hr. After that, $NaBH(OAc)_3$ (33.2 mg, 156 umol) was added one portion. The resulting reaction mixture was stirred at -15 °C for 1 hr. On completion, the mixture was quenched with H_2O (0.5 mL) at 0 °C and concentrated under reduced pressure to afford a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10um; mobile phase: [water (0.225%FA)-ACN]; B%: 22%-52%, 10 min) to give the title compound (31.8 mg, 46% yield) as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 10.88 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.44 (s, 1H), 7.43 - 7.37 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 5.18 (s, 1H), 4.31 - 4.16 (m, 2H), 3.70 - 3.66 (m, 4H), 2.85 - 2.76 (m, 2H), 2.70 - 2.63 (m, 1H), 1.85 - 1.81 (m, 2H), 1.73 - 1.67 (m, 6H), 1.63 - 1.56 (m, 2H), 1.49 (s, 9H). LC-MS (ESI$^+$) *m/z* 872.4 (M+H)$^+$.

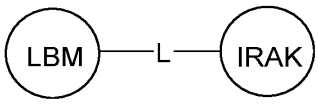
* * * * * *

[001168] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

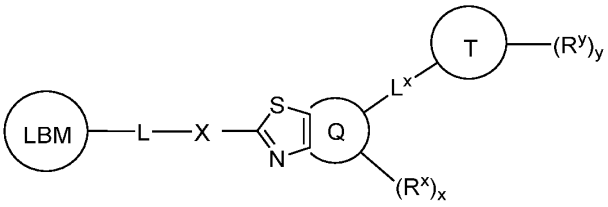
1. A compound of formula **I**:



I

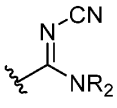
or a pharmaceutically acceptable salt thereof, wherein:

IRAK is an IRAK binding moiety capable of binding to IRAK4, said compound of formula **I** is a compound of formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

each R^x is independently hydrogen, deuterium, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-N^+(O^-)R_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-P(O)R_2$, $-SiR_3$, $-Si(OR)R_2$, or 

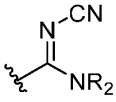
; or

two R^x groups are optionally taken together to form an optionally substituted 5-6 membered partially unsaturated or aryl fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from

nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, deuterium, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-SiR_3$, $-SF_5$, or  ;

each R^z is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring Q is selected from benzo or a fused 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring T is selected from phenyl, a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring T is further optionally substituted with 1-2 oxo groups;

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-Cy^x-$, -O-, -S-, -C(O)-, -C(S)-, $-CR_2-$, -CRF-, $-CF_2-$, -NR-, -N=CR-, -CR=CR-, or $-S(O)_2-$, wherein R of $-CR_2-$, -CRF-, -NR-, -N=CR-, or -CR=CR- can combine with R^x or R^y to form a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

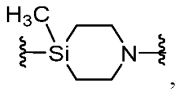
$-Cy^x-$ is an optionally substituted ring selected from a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein $-Cy^x-$ is optionally substituted with 1-2 oxo groups;

X is a covalent bond or an optionally substituted bivalent ring selected from phenylenyl, a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclylenyl or heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

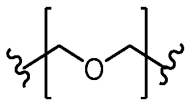
x is 0, 1, 2, 3 or 4;

y is 0, 1, 2, 3 or 4;

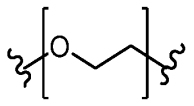
L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –C(D)(H)-, -C(D)$_2$–, –Cy-, -O-, -N(R)-, –Si(R)$_2$–, –Si(OH)(R)–, –Si(OH)$_2$–, –P(O)(OR)–, –P(O)(R)–, –P(O)(NR$_2$)–, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)$_2$-, -N(R)S(O)$_2$-, -S(O)$_2$N(R)-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, –N(R)C(O)O-,



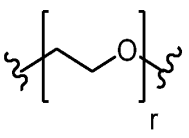
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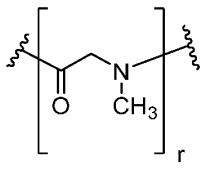
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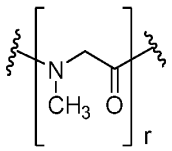
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,



, or



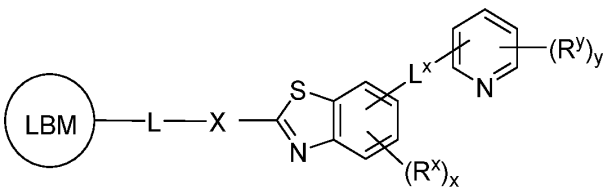
;

each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-7 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

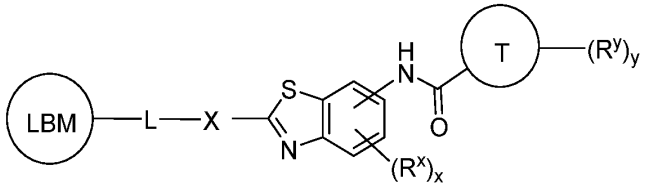
r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

LBM is an IMiD-based cereblon E3 ubiquitin ligase binding moiety.

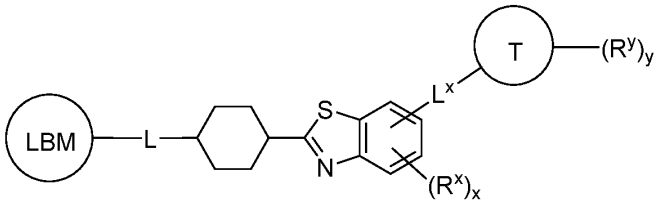
2. The compound of claim 1, wherein said compound is selected from any one of the following formulae:



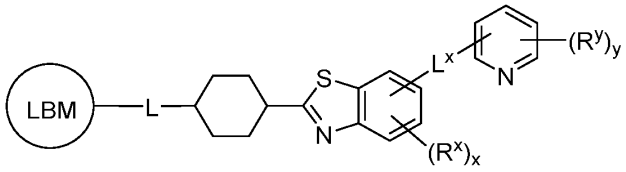
I-a-1



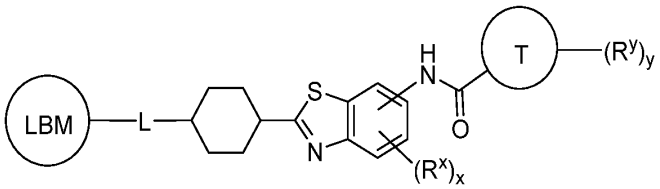
I-a-2



I-a-3



I-a-4

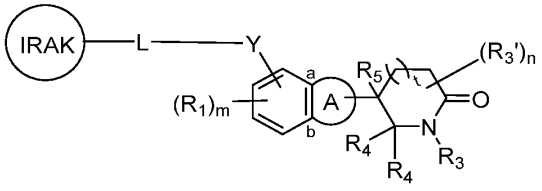


I-a-5

or a pharmaceutically acceptable salt thereof.

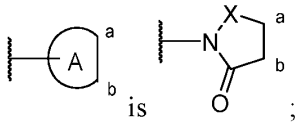
3. The compound of claim 4, wherein the IMiD-based cereblon E3 ubiquitin ligase binding moiety is selected from any one of the following formulae:

(*i*)



I-oo-1

or a pharmaceutically acceptable salt thereof, and wherein:



is ;

Y is a bond;

X is C(O) or CH_2;

each R_1 is independently hydrogen, halogen, C_1-C_4 alkyl, or C_1-C_4 alkoxy;

R_3 is hydrogen;

two R_4, together with the carbon atom to which they are attached, form C(O);

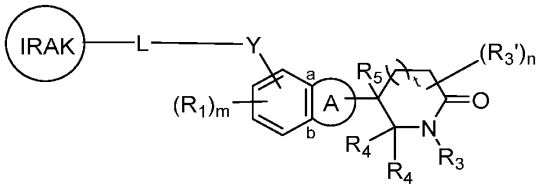
R_5 is hydrogen or C_1-C_3 alkyl;

t is 1;

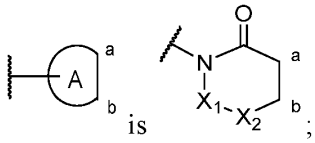
m is 0, 1, 2, 3, or 4; and

n is 0;

(*ii*)



I-oo-1



is ;

Y is a bond;

X_1-X_2 is C(H)=N, C(C_1-C_4 alkyl)=N, or C(C_1-C_4 haloalkyl);

each R_1 is independently hydrogen, halogen, -NH_2, -OH, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkoxy;

R_3 is hydrogen;

two R_4, together with the carbon atom to which they are attached, form C(O);

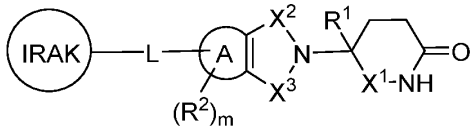
R_5 is hydrogen or C_1-C_3 alkyl;

t is 1;

m is 0, 1, 2 or 3; and

n is 0; or

(*iii*)



I-ccc-1

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is –C(O)–;

X^2 is –C(O)–;

X^3 is $–CH_2–$ or –C(O)–;

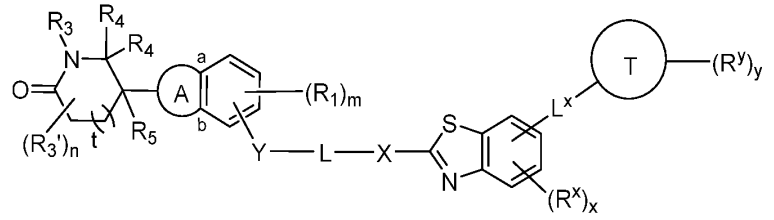
R^1 is hydrogen or C_{1-4} aliphatic;

each of R^2 is independently hydrogen, halogen, C_{1-4} aliphatic or $–OC_{1-4}$ aliphatic;

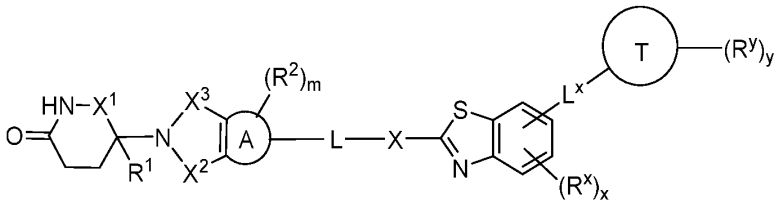
Ring A is benzo; and

m is 0, 1, 2, 3 or 4.

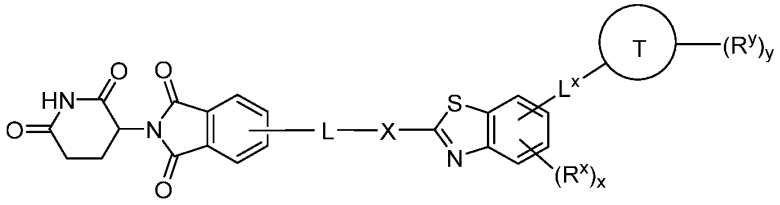
4. The compound of claim 3, wherein said compound is selected from any one of the following formulae:



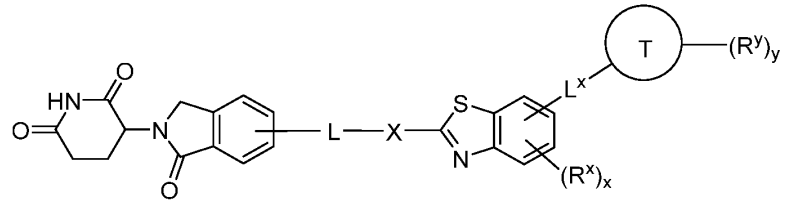
I-a-6



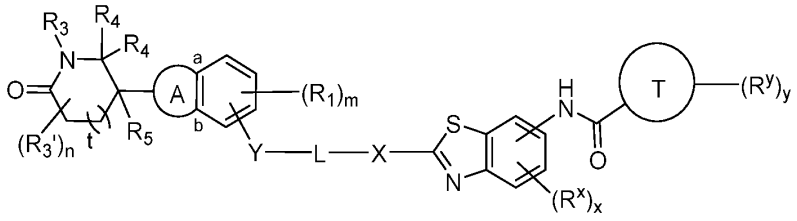
I-a-7



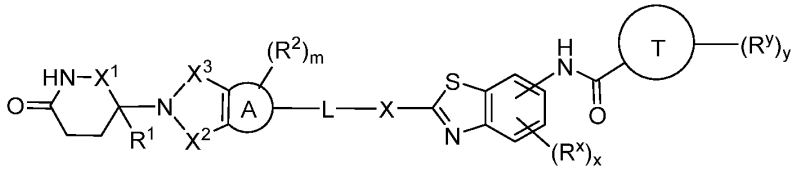
I-a-8



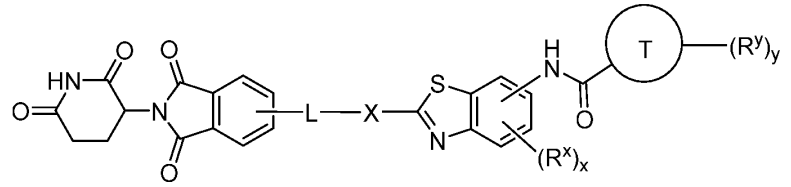
I-a-9



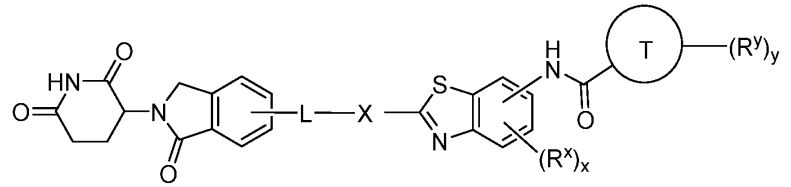
I-a-10



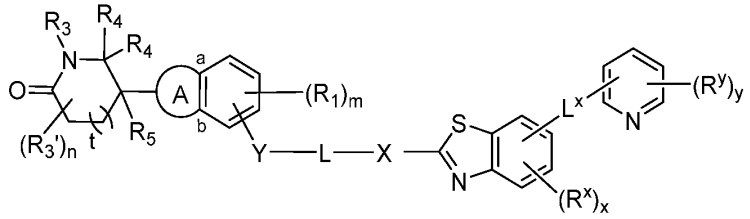
I-a-11



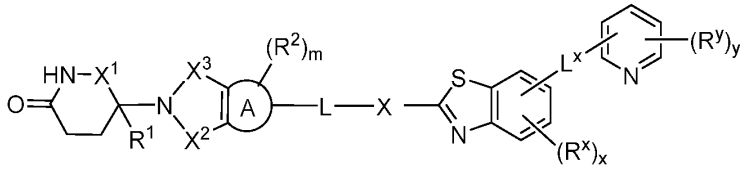
I-a-12



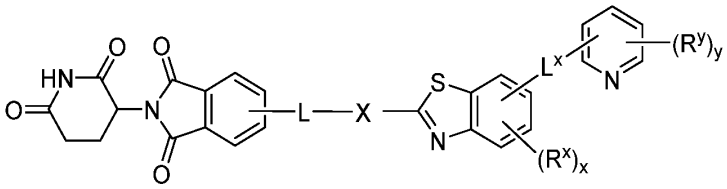
I-a-13



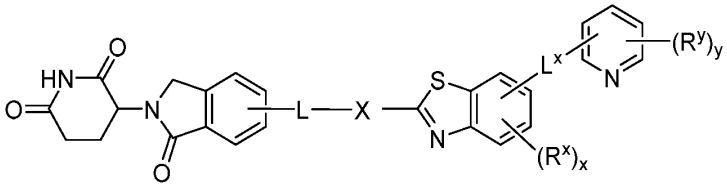
I-a-14



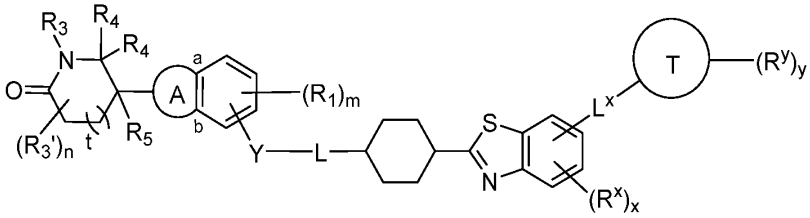
I-a-15



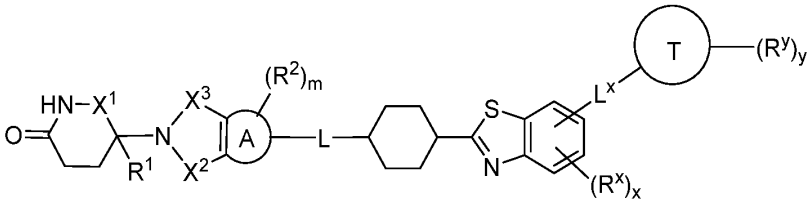
I-a-16



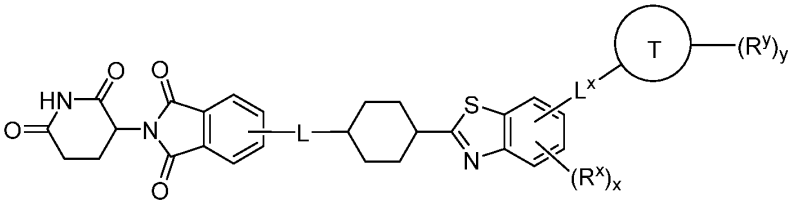
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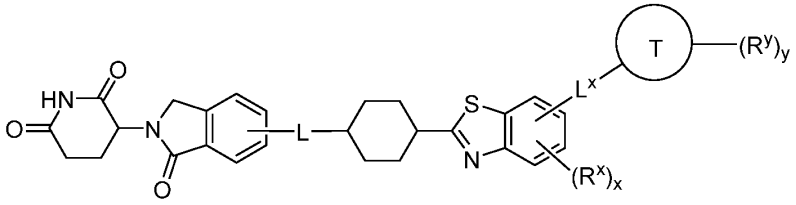
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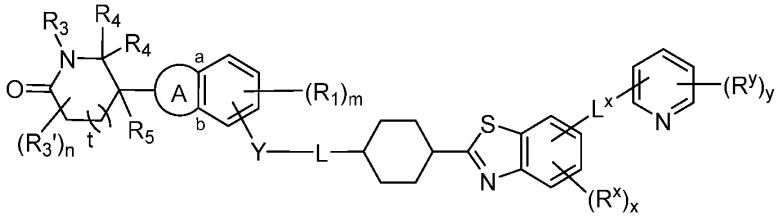
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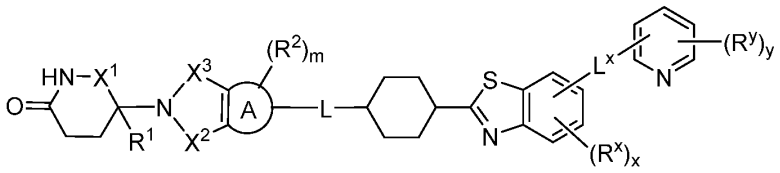
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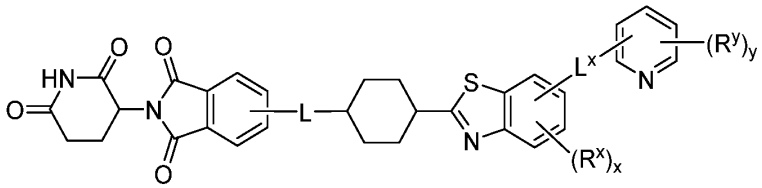
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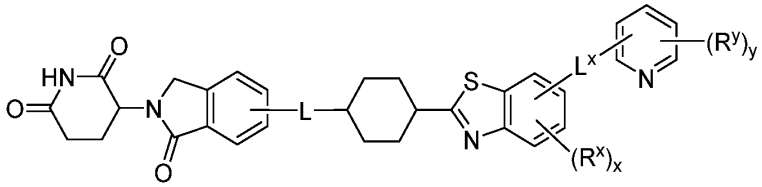
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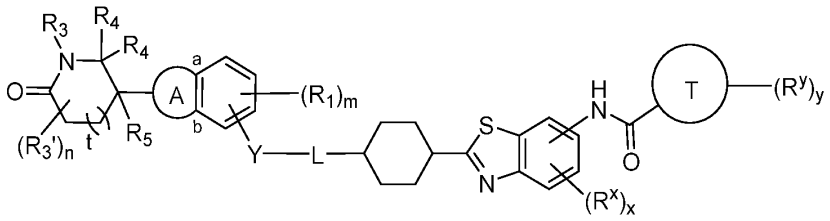
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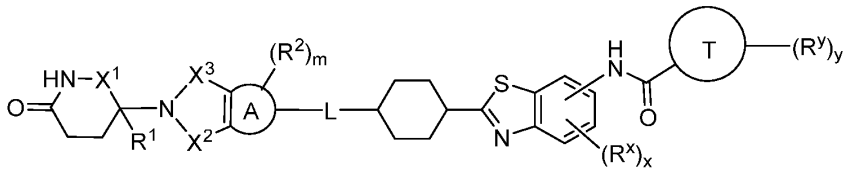
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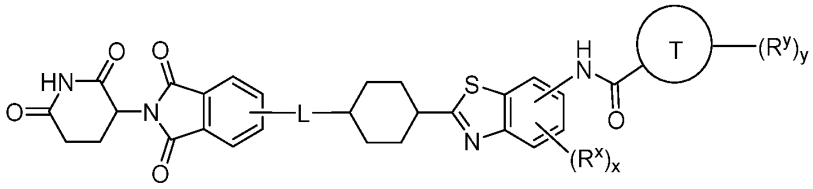
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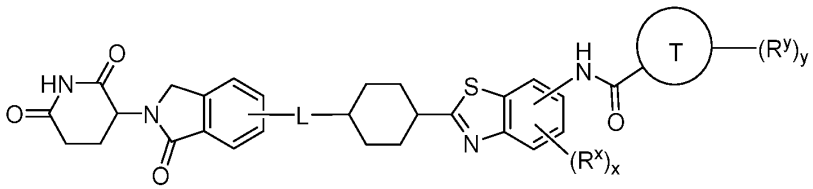
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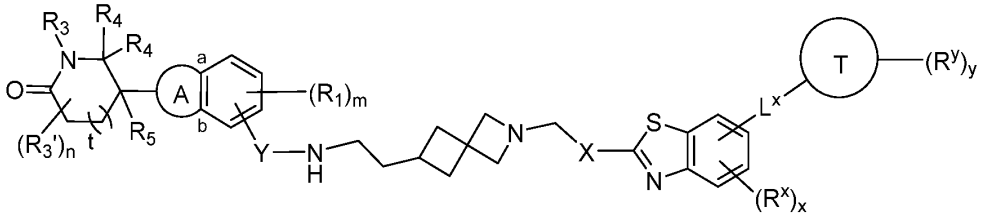
I-a-27



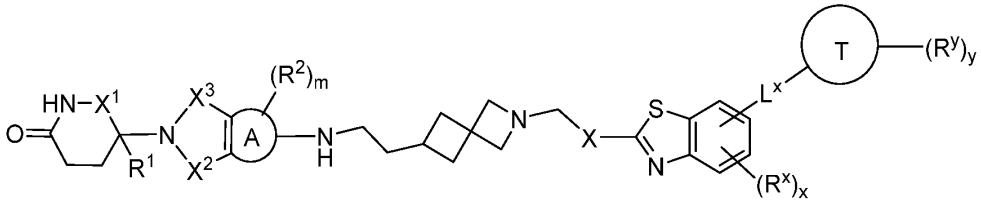
I-a-28



I-a-29



I-a-30



I-a-31

or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1-4, wherein L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -N(R)-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -N(R)$S(O)_2$-, -$S(O)_2$N(R)-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, –N(R)C(O)O-.

6. The compound of any of one of claims 1-5, wherein said compound is selected from any one of the compounds depicted in **Table 1**, or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a compound according to any of one of claims 1-6, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

8. The pharmaceutical composition according to claim 7, further comprising an additional therapeutic agent.

9. A method of degrading IRAK4 protein kinase in a patient or biological sample comprising administering to said patient, or contacting said biological sample with a compound according to any of one of claims 1-6, or a pharmaceutical composition thereof.

10. A method of treating an IRAK4-mediated disorder, disease, or condition in a patient comprising administering to said patient a compound according to any of one of claims 1-6, or a pharmaceutical composition thereof.

11. The method according to claim 10, further comprising administration of an additional therapeutic agent.

12. The method according to claim 10, wherein the IRAK4-mediated disorder, disease or condition is a cancer or proliferative disorder selected from benign or malignant tumor, solid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastoma, neuroblastoma, multiple myeloma, gastrointestinal cancer, colon carcinoma, colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation,

psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphoma, Hodgkin's or Non-Hodgkin's_lymphoma, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, an IL-1 driven disorder, a MyD88 driven disorder, smoldering or indolent multiple myeloma, and a hematological malignancy selected from leukemia, diffuse large B-cell lymphoma (DLBCL), ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, plasmacytoma, and intravascular large B-cell lymphoma.

13. The method of claim 12, wherein the MyD88 driven disorder is selected from ABC DLBCL, Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma, and chronic lymphocytic leukemia.

14. Use of a compound according to any one of claims 1-6 or a pharmaceutical composition thereof in the manufacture of a medicament for treating an IRAK4-mediated disorder, disease, or condition in a patient in need thereof.

15. The use according to claim 14, further comprising an additional therapeutic agent.

16. The use according to claim 14, wherein the IRAK4-mediated disorder, disease or condition is a cancer or proliferative disorder selected from a benign or malignant tumor, solid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastoma, neuroblastoma, multiple myeloma, gastrointestinal cancer, colon carcinoma, colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphoma, Hodgkin's or Non-Hodgkin's_lymphoma, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, an IL-1 driven disorder, a MyD88 driven disorder, smoldering or indolent multiple myeloma, and a hematological malignancy selected from_leukemia, diffuse large B-cell lymphoma (DLBCL), ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt

lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, plasmacytoma, or intravascular large B-cell lymphoma.

17. The use of claim 16, wherein the MyD88 driven disorder is selected from ABC DLBCL, Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma, and chronic lymphocytic leukemia.